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SYMPOSIUM ON THE MECHANISM AND MANAGEMENT OF HEMORRHAGIC DISORDERS IN CHILDREN

PART II

GUEST EDITOR—I. NEWTON KUGELMASS, M.D., PH.D., SC.D.

The Investigation and Treatment in Childhood of the Hereditary Hemorrhagic Disorders — R. M. HARDISTY AND G. I. C. INGRAM

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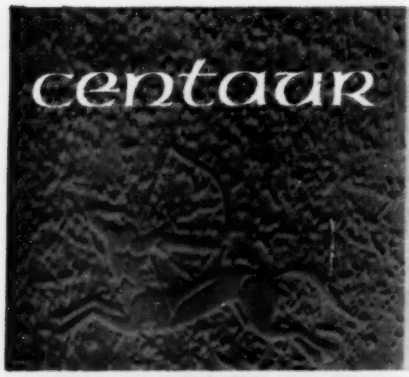

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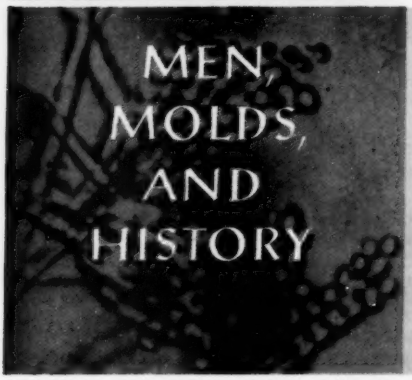

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Symposium on the Mechanism and Management of Hemorrhagic Disorders in Children

PART II

GUEST EDITOR—I. NEWTON KUGELMASS, M.D., Ph.D., Sc.D.

The Investigation and Treatment in Childhood of the Hereditary Hemorrhagic Disorders

R. M. Hardisty and G. I. C. Ingram

THE HOSPITAL FOR SICK CHILDREN, GREAT ORMOND STREET, AND ST. THOMAS' HOSPITAL LONDON, ENGLAND

Ars artis celare artem, and good organization conceals its own efficiency. This is certainly true of the hemostatic mechanism, which we usually take for granted until it fails us. It is, in fact, a closely integrated system of some complexity, with three groups of components: the blood vessels, the platelets, and the clotting reactions. Defective hemostasis may result from an acquired, and usually temporary, breakdown in the system or from one of a number of lifelong inborn disorders; the latter group includes the hereditary bleeding diseases with which this article deals.

HEMOSTATIC COMPONENTS IN THE PLASMA

These disorders are all due to a deficiency of one or occasionally more of the plasma factors involved in hemostasis. Nearly a dozen of these are now recognized. Figure 1 shows the sequence in which we believe the clotting factors interact when venous blood is allowed to coagulate in a glass tube. A somewhat different course of events follows when blood is clotted by tissue juice (fig. 2). Isolated congenital deficiencies of each of the plasma factors represented in these two illustrations have been described, and each of these deficiencies, excepting only that of Hageman factor, has been found to result in an abnormal bleeding state. It will be apparent that antihemophilic factor (factor VIII) and plasma thromboplastin component (factor IX) only are involved in spontaneous clotting, whereas factor VII is only involved in

Part I of this Symposium appeared in the August issue.

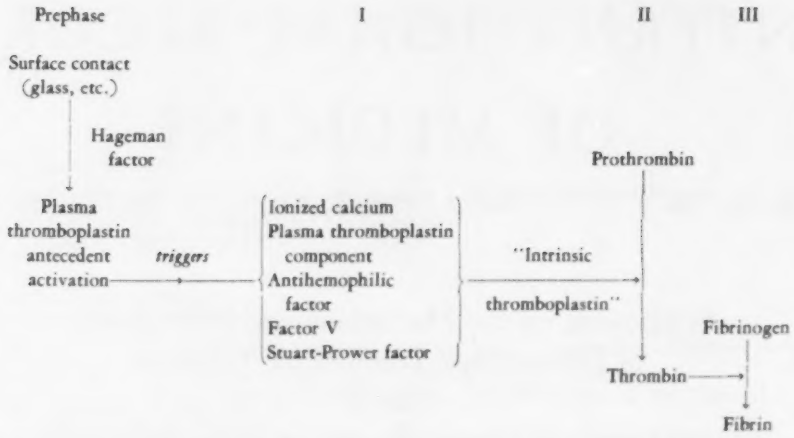

FIG. 1. The sequence of events when blood clots spontaneously in vitro through the formation of intrinsic thromboplastin. The prephase represents an initiating mechanism, which triggers off the serial interaction of the components of phase I (which includes also a platelet phospholipid not shown here); the final product of this stage, which we term "intrinsic thromboplastin," converts prothrombin to thrombin (phase II), and this in turn polymerizes fibrinogen to fibrin (phase III).

coagulation by tissue juice. Now, since a deficiency of any one of these leads to abnormal bleeding, we must conclude that both the intrinsic and the extrinsic thromboplastin systems are required for normal hemostasis.

An exact differentiation cannot be made clinically between the bleeding states arising from deficiencies of different clotting factors, and the exact diagnosis depends on laboratory tests. Although the natural history of all these conditions is very similar, the fundamental treatment is to replace by intravenous infusion the particular component that is missing from the plasma, so that an accurate distinction

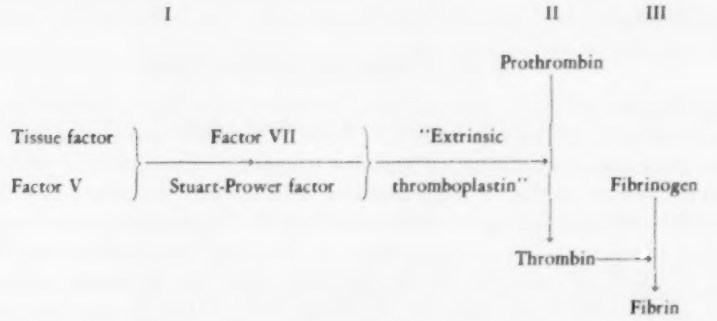

FIG. 2. The sequence of events when blood is clotted by the addition of tissue juice, forming "extrinsic thromboplastin." Here there is no prephase, but phase I, the formation of extrinsic thromboplastin, begins at once through the interaction of tissue factor and factor V, the rate of this reaction being governed by factor VII and Stuart-Prower factor. Phase II and phase III are the same as in figure 1.

is of great importance. As a matter of fact, the majority of cases are due to deficiencies of antihemophilic factor or plasma thromboplastin component. In Great Britain, for instance, out of a population of some 50 million, there are probably a few thousand cases of these bleeding disorders; of 1331 cases so far notified to the Central Haemophilia Register, maintained by the Medical Research Council, 1,094 (82 per cent) have been found to be hemophilia and 196 (15 per cent) Christmas disease (plasma thromboplastin component deficiency), while the remaining 41 (3 per cent) are either mixed deficiencies or deficiencies of other factors.

Among this residuum of rarities, there is the interesting condition called von Willebrand's disease, which appears to be due to deficiency of a plasma factor required not in the clotting sequence, but for a normal vascular response to injury, and in some cases this is associated with a partial deficiency of antihemophilic factor. This disease is distinct from hereditary hemorrhagic telangiectasia, in which abnormal bleeding may occur only from the telangiectases (e.g., in the nose) with normal hemostasis elsewhere.

FAMILY PATTERNS

These disorders are familial and it is sometimes possible to recognize characteristic modes of inheritance. For instance, hemophilia and Christmas disease are sex-linked and recessive, so that the disorders affect males but are transmitted through heterozygous females who are known as "carriers." A typical pedigree of hemophilia is shown in figure 3.

In fact, all the daughters of a hemophilic person will be carriers, but on the average only half the sons of a carrier will be affected and only half her daughters will be carriers in their turn. The carrier state can thus be passed from mother to daughter for several generations with no affected males. Unfortunately, we still have no certain way of distinguishing carriers from genetically normal women, although a proportion of carriers appear to have a slightly reduced level of antihemophilic factor; such a finding in a female member of a hemophilic family will slightly increase the chance that she may be a carrier, but an antihemophilic factor level within the normal range is of negligible significance in genetic prognosis. The same considerations may be taken to apply as a rule in plasma thromboplastin component

FIG. 3. A typical pedigree of hemophilia. Black squares indicate affected males. Circles with a dot in the center indicate carrier females.

deficiency, though there is evidence that the gene responsible for this condition may not always be completely recessive, in that female carriers occasionally suffer from a mild bleeding tendency, associated with a slightly reduced level of plasma thromboplastin component in the blood.

In practice, the family history proves negative in some 40 to 50 per cent of cases of these two conditions, either because the disease has been transmitted through several generation of carriers, without known affected male relatives, or because it has arisen from a new mutation.

The genetics of the rarer disorders are less well known, but it seems that both plasma thromboplastin antecedent deficiency and von Willebrand's disease are transmitted as autosomal dominants.

CLINICAL DIAGNOSIS

The problem of diagnosis of this group of conditions may be considered at two levels: first, whether a child has a hereditary bleeding disorder at all, and second, the exact diagnosis. Since all the coagulation disorders have essentially similar symptomatology, the answer to the second question can be provided only by laboratory tests, but the first depends as much on clinical as on laboratory methods for its answer. A full and accurate clinical history of the patient and his family usually provides the best indication of a bleeding tendency as well as of the congenital nature of the condition and may be of much help in indicating the type of laboratory investigation to be carried out initially. In taking a history, enquiry must be made for spontaneous bleeding and bruising as well as for excessive hemorrhage after trauma, whether surgical or accidental; in the latter context, two points in particular should be borne in mind. First, it is the duration of bleeding that is of significance and not the amount of blood lost, which depends simply on the extent of the injury. Second, it is important to inquire whether the patient has ever been injured or undergone surgery without excessive bleeding; such incidents are often overlooked by the patient and his relatives, but they provide a better indication of normal hemostatic function than any laboratory investigation and may help to date the onset of a bleeding disorder.

The coagulation deficiency states vary widely in their clinical severity from one patient to another, but the severity of the condition usually remains remarkably constant in any one person throughout his lifetime, and throughout the affected members of a single family, at least as far as hemophilia and plasma thromboplastin component deficiency are concerned. In hemophilia, there is good correlation between the degree of clinical severity and the plasma antihemophilic factor level, and a similar relationship probably obtains in the other deficiency states, which have been less extensively studied by quantitative assay procedures. Thus a person with severe hemophilia, having less than 1 per cent of average normal antihemophilic factor, is likely to suffer from apparently spontaneous hemorrhages such as hemarthroses, and to develop large, deep hematomas after trivial injuries, from early childhood. At the other end of the scale, mild hemophilia, with 10 to 20 per cent antihemophilic factor, may result only in prolonged bleeding after surgical oper-

ations, tooth extraction, and serious injury; we have seen several men with mild hemophilia who reached middle age before requiring investigation and treatment.

It follows that cases presenting in childhood are likely to be of at least moderate severity. Even the most severe cases, however, often escape detection until the child starts to crawl or walk, unless he is circumcised in infancy. Thus the pattern of hemorrhages differs markedly from that which results from disorders of the platelets or blood vessels, in which widespread spontaneous hemorrhages into the skin and mucous membranes are the rule. In von Willebrand's disease, the functional vascular defect often results in apparently spontaneous hemorrhages, particularly from the nose; excessive postoperative bleeding is also a common presenting symptom in this condition, which often appears to run a fluctuating course, so that surgery or tooth extraction may on occasion be performed without mishap and at other times be followed by prolonged bleeding.

LABORATORY TESTS

In regard to laboratory tests, here again the diagnostic problem may be viewed at two levels: Has the patient a constitutional bleeding disorder, and if so, what is its nature? To answer the first question, one must examine the platelets and test the functional adequacy of the small vessels and of both the extrinsic and intrinsic coagulation systems. Screening tests for this purpose should be sensitive but not highly specific. In practice, the tests used are, respectively, the platelet count and appearances in stained films; the bleeding time; the one-stage prothrombin time; and the thromboplastin generation test[1] or one of its modifications (e.g., the thromboplastin screening test[2]). A somewhat less sensitive test of the intrinsic coagulation system is the prothrombin consumption test in one of its many forms. Although the whole-blood clotting time is prolonged in moderate and severe disorders of the intrinsic system, it is altogether too insensitive to be used as the sole screening test of this system; a normal whole-blood clotting time is found in about one third of cases of hemophilia and cannot therefore be held to exclude a disorder of coagulation.

The results obtained by the use of the three screening tests recommended in various hereditary bleeding disorders are shown in table I. The platelet count will of course be normal in each case.

To determine the exact nature of a coagulation defect, specific assay procedures for the relevant coagulation factors should be used. These consist, in principle, of testing the ability of the patient's plasma to correct the clotting defect, in an appropriate system, of plasma having a known defect; the details will not be considered here.

Tests of the clotting mechanism are usually carried out on venous blood, and for accurate quantitative results, a clean venipuncture is a *sine qua non*. In infants and small children, however, it may be technically difficult as well as disturbing to the patient to obtain blood in this way, and at this age, reasonably accurate tests of the intrinsic and extrinsic clotting systems can be carried out on capillary blood, provided that it is taken rapidly into a suitable anticoagulant solution. If 0.1 ml. of blood is taken into 0.9 ml. of saline containing 0.2 per cent sodium citrate, and

TABLE I

Results of Screening Tests

Diagnosis	Bleeding time	One-stage prothrombin time	Thromboplastin generation test
Hemophilia (antihemophilic factor deficiency)	Normal	Normal	Adsorbed plasma defective
Plasma thromboplastin component deficiency	Normal	Normal	Serum defective
Plasma thromboplastin antecedent deficiency	Normal	Normal	Adsorbed plasma and serum defective
Factor V deficiency	Normal	Prolonged	Adsorbed plasma defective
Factor VII deficiency	Normal	Prolonged	Normal
Stuart-Prower factor deficiency	Normal	Prolonged	Serum defective
Congenital afibrinogenemia	Normal	Plasma incoagulable	Normal
Von Willebrand's disease	Inconstantly prolonged	Normal	Usually normal; plasma may be defective

centrifuged, the resulting diluted plasma can be tested in various appropriate assay systems, and a specific diagnosis can thus be reached with a minimum of trauma to the child; it has proved possible to detect even mild hemophilia, with antihemophilic factor concentrations up to 30 per cent, by this technique.[2]

MANAGEMENT

The principles of management of the congenital disorders of coagulation are the avoidance of unnecessary physical trauma and the use of appropriate replacement therapy and of local measures when bleeding occurs.

Prophylaxis. The life of every child with one of these disorders must be tempered to the severity of his disease; while some children require the protection of special schools for the physically handicapped, others may find from experience that they can play strenuous games with impunity. Surgery and tooth extractions are best avoided in every case whenever possible and may constitute a real danger to life in severe cases. For this reason regular conservative dentistry is essential, to obviate the need for extractions. A not uncommon problem is that of the acute abdomen in a boy with hemophilia; the likelihood that apparent acute appendicitis is, in reality, retroperitoneal hemorrhage must always be borne in mind, and the temptation to carry out an exploratory laparotomy resisted.

Local Treatment. Whenever the bleeding point is accessible, as for example in the case of a tooth socket, firm but gentle pressure should be applied. For this purpose, an absorbable dressing soaked in thrombin is best used. Thrombin will clot blood lacking any clotting factor but fibrinogen, but a continuing flow of blood will wash away any clot formed, and the action of the thrombin must therefore be supplemented not only by gentle pressure but, more importantly, by replacement therapy.

Thrombin will be ineffective in von Willebrand's disease, in which the main defect is a vascular one, but local pressure and the use of vasoconstrictor substances such as epinephrine play a part in the control of bleeding in this condition. Tight suturing of the wound edges must obviously be avoided in all these conditions.

For tooth extractions, protection should be afforded to the tooth socket by means of a previously prepared closely fitting dental splint, beneath which an absorbable dressing is held in place, the whole remaining undisturbed for several days after extraction.

Local measures are seldom of much avail in the treatment of internal bleeding, but good results have been obtained by the aspiration of hemarthroses followed by pressure bandaging of the joint; these measures should always be covered by replacement therapy.

General Treatment. This consists of correction of the specific defect by intravenous administration of whole blood, plasma, or a partially purified preparation of the appropriate plasma component. Because of the short survival of all the clotting factors, and the necessity of giving large quantities of them if they are to be raised to an effective level in the patient's plasma, maintenance therapy is out of the question at present, and replacement therapy must be reserved for the treatment of bleeding episodes and to prevent excessive hemorrhage when surgery is undertaken.

As antihemophilic factor is notoriously labile on storage, it is essential that blood or plasma used in the treatment of hemophilia should be no more than a few hours old. Plasma thromboplastin component is more stable in vitro, but it is found in practice that fresh plasma is also more effective than stored in the treatment of plasma thromboplastin component deficiency; it is in fact the agent of choice for the control of bleeding episodes in all the rarer congenital defects of coagulation, except for afibrinogenemia, for which purified human fibrinogen can be given in concentrated form.

The work of Nilsson and her colleagues[5] suggests that von Willebrand's disease is due to deficiency of a plasma factor, present in Cohn's fraction I, which is required for normal vascular function; bleeding in this condition can be controlled and the bleeding time and associated antihemophilic factor deficiency corrected by transfusion of fresh plasma or fraction I.

Much work has been devoted in recent years to the purification of antihemophilic factor for therapeutic use, and Macfarlane and his collaborators[4] have had considerable success with highly concentrated preparations from ox and pig plasma. A few milliliters of one of these preparations will raise a patient's plasma antihemophilic factor to normal levels, but the development of species-specific antibodies precludes the use of each for more than 10 to 14 days. For this reason, they must be reserved for use in serious injury or major surgery, when the very large volumes of plasma required for effective replacement therapy may overtax the patient's circulation and the resources of the blood bank.

When high blood antihemophilic factor levels are required in pediatric practice, circulatory overloading and the technical difficulties of administering large volumes of fluid may also be avoided by the use of purified human antihemophilic factor, but it is unlikely that this will ever be available in sufficient quantity to permit its use

for all hemophilic subjects. Concentrated human plasma fractions containing plasma thromboplastin component have been used in the treatment of plasma thromboplastin component deficiency.

Replacement therapy in hemophilia should always be carefully controlled by repeated antihemophilic factor assays. Throughout surgical operations, and for several days afterward, until firm wound healing has occurred, the aim should be to maintain the plasma antihemophilic factor at 20 per cent of normal or more; in practice this may mean transfusing up to half the patient's plasma volume of fresh plasma daily or a proportionately smaller volume of a concentrated preparation. In the treatment of hematomas and hemarthroses, it is seldom necessary to aim above about 10 per cent, and repeated transfusion is not usually required. Such spontaneous tissue hemorrhages can therefore be effectively treated with whole plasma, and concentrated preparations can be reserved for major surgery and serious accidents.

Similar considerations apply to plasma thromboplastin component deficiency and the rarer deficiency states, but the quantitative aspects are less firmly based. Plasma thromboplastin antecedent deficiency is usually relatively mild, and clinical experience suggests that patients with this disorder seldom require transfusion except when undergoing surgery or tooth extraction and that relatively small amounts of fresh blood or plasma will then usually suffice.

It is possible that the further purification and isolation of antihemophilic factor from animal sources will eventually make regular replacement therapy as simple in hemophilia as is insulin therapy for the diabetic person. Meanwhile, the therapeutic advances of recent years give no cause for despondency to people with this disease.

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Management of Hemorrhagic Diseases in Children*

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PLATELET DISORDERS

Hereditary thrombocytopenia is a quantitative platelet defect in certain families. There are relatively few platelets, usually less than 20,000, but the platelets are qualitatively very effective, dissociating rapidly unless there is intercurrent infection or systemic disease. Hemorrhagic episodes are controlled with fresh blood transfusions, but splenectomy is contraindicated.

Congenital thrombocytopenia is due to the passage across the placental carrier of maternal antiplatelet antibodies. They may be derived from a previously purpuric mother or from antiplatelet antibodies in an infant whose platelet type differs from that of the mother isoimmunized by a heterospecific platelet transfusion or pregnancy. The condition is rare but mild and subsides spontaneously. Severe neonatal thrombocytopenia due to isoantibodies must be treated by platelet or exchange transfusions.

Neonatal thrombocytopenia may accompany severe prenatal or postnatal infection, especially syphilis, septicemia, toxoplasmosis, torulosis, or cytomegalic inclusion disease; blood diseases, especially congenital aplastic anemia, congenital leukemia and congenital absence of megakaryocytes; and giant hemangioma causing sequestration of platelets within its extensive vascular bed. Thrombotic thrombocytopenic purpura accompanied by hemolytic anemia, splenomegaly, hepatomegaly, and mental and neurological manifestations is usually fatal.

Idiopathic thrombocytopenic purpura occurs in the acute self-limited or chronic recurrent form as spontaneous small hemorrhages into the skin, mucous membranes, and other tissues. In the acute form the onset is sudden and severe after an infection and in the chronic form, latent and mild as a distinct entity. Blood platelets may be decreased to less than 10,000/cu. mm. but bone marrow megakaryocytes are normal or increased in number. The bleeding time is prolonged and the tourniquet test is positive because of failure of capillaries to retract and the lack of platelets to plug the openings of bleeding vessels. Clotting time is normal because few platelets are necessary to initiate clotting. Clot retraction is delayed and incomplete because considerable numbers of platelets are required for syneresis. The prothrombin consumption test shows defective platelet utilization.

Platelet deficiency appears to be due to plasma factors of an immunological process since the life span of normal platelets infused into the patient is markedly decreased while the life span of transfused platelets is normal in thrombocytopenia due to

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bone marrow hypoactivity. Splenectomy produces striking improvement; hence the spleen removes sensitized platelets and produces platelet agglutinin. The toxin affects both platelets and capillary endothelium, which are antigenically similar, resulting in antibody production for these injured tissues.

Purpura may be controlled by direct transfusions of whole blood, freshly drawn at two- to five-day intervals from platelet-rich polycythemic donors. This will temporarily improve the platelet level, bleeding time, and cell volume. Kugelmass[24] found that platelet transfusions with siliconized apparatus and ethylenediaminetetraacetic acid as anticoagulant are most effective, but repeated injections may lead to the development of platelet agglutinins and decrease survival time of transfused platelets. Fresh blood with normally dispersed platelets should be used for thrombocytopenia and stored blood with agglutinated platelets for blood replacement. When transfusions fail to control bleeding in the acute fulminating or chronic recurrent case, ACTH or cortisone is effective not only in the temporary emergency of a serious hemorrhage but in preoperative preparation for splenectomy. There may be a remission in the thrombocytopenia and an improvement in capillary resistance.

Splenectomy should be considered a lifesaving procedure during the quiescent stage of the disease to remove the splenic factor responsible for the low platelet levels, provided sternal marrow smears reveal adequate numbers of megakaryocytes. After splenectomy, bleeding ceases dramatically in two thirds of the chronic cases, and the platelets rise to high levels for a week or two before falling to normal or low levels. The bleeding time is more favorably affected than the number of platelets or the retractility of the clot; hence splenectomy improves capillary resistance. Serial blood transfusions may be necessary when hyperfunctioning reticuloendothelial phagocytes are present in the liver and lymph nodes. Splenectomy is contraindicated if the blood picture suggests aplasia with severe anemia and neutropenia or if the marrow shows diminished platelets and/or megakaryocytes.

Symptomatic thrombocytopenia is more common than the essential type of purpura. It is characterized by low platelet levels incidental to some underlying disease in the bone marrow or spleen. The bone marrow defect should be treated in aplastic anemia since all parts of the marrow, including the megakaryocytes, are affected. Severe secondary purpura from markedly reduced platelets responds to supportive replacement of fresh citrated blood, polycythemic blood being most effective and bank blood, least. In hypoplastic anemia accompanying gastrointestinal or allergic disorders, there may be platelet deficiency from marrow hypoplasia. Secondary purpura will clear promptly with correction of the nutritional deficiency in amino acids, liver extract, vitamin B and C complexes, trace minerals, and polyunsaturated fatty acids. In displacement thrombocytopenia accompanying leukemia, myeloma, metastatic carcinoma, etc., there is an obliteration of megakaryocytes and other bone marrow elements, detected by bone marrow aspiration and controlled by fresh blood transfusions, ACTH and cortisone, and specific treatment of the primary marrow disorder.

In toxic thrombocytopenia, damage to megakaryocytes in the marrow reduces circulating platelets in acute infections, chemical poisoning, drug and food allergy,

irradiation, insect bites, and burns. The condition is detected by supravital staining of fresh marrow and controlled by fresh blood transfusions, hesperidin, 100 mg., ascorbic acid, 500 mg. daily, and specific treatment of underlying disease. The splenic defect should be corrected in secondary thrombocytopenia due to hypersplenism. The enlarged spleen becomes overactive in the destruction of platelets, but the marrow shows an increase in mature megakaryocytes with normal platelet formation. An epinephrine test confirms platelet hypersequestration in the spleen in Banti's disease, Felty's syndrome, Gaucher's disease, splenic Hodgkin's granuloma, congestive splenomegaly, myocardial decompensation, and acute infectious splenic tumor, each of which responds to emergency splenectomy.

Platelet Excess. Thrombocytosis occurs normally at high altitudes or after severe exercise and pathologically in malnutrition, rheumatic fever, suppurative infection, polycythemia, hemolytic anemia, chronic myelogenous leukemia, platelet thrombosis, and embolism. Moulten[27] demonstrated thromboembolism to be due primarily to increased adhesiveness of platelets from degradation products of living tissues and secondarily to increased blood coagulability, venous stasis, and vascular injury.

HEMOPHILIA SYNDROMES A, B, C, AND D

Antihemophilic globulin deficiency (hemophilia A) or classical hemophilia in the male is transmitted as a sex-linked recessive trait. The condition involves a lifelong tendency to excessive hemorrhage into the skin, mouth, gastrointestinal tract, and joints. Hemophilia A is transmitted by daughters of hemophilic men to their sons. Absence of the specific enzyme controlled by the mutant gene decreases antihemophilic globulin synthesis; hence the severity of the disease varies inversely with the antihemophilic globulin titer. This may range from 0 to 30 per cent, in comparison with the normal 65 to 135 per cent. The mild allelic form is not completely recessive since female carriers bruise easily and develop menorrhagia. Hemophilia is characterized by the very slow conversion of prothrombin to thrombin in shed blood. The rate is greatly accelerated in vivo after blood transfusion and in vitro after addition of normal plasma to hemophilic blood. The amount of prothrombin consumed in clotting hemophilic blood is a direct function of the amount of antihemophilic globulin added from any source. Graham et al[11] found that plasma antihemophilic globulin is not adsorbed by barium sulfate.

Antihemophilic globulin is present in normal plasma in association with globulin and fibrinogen or more specifically with fractions I, III_1, and III_2. It is consumed during blood coagulation, especially during thromboplastic generation. The clotting time of blood is normal if the concentration of plasma antihemophilic globulin is 30 per cent of normal or more and is greatly prolonged with decreasing concentrations. But bleeding does not commence until the plasma antihemophilic globulin level falls below the critical 10 per cent of normal, as in true hemophilia. Antihemophilic globulin is extremely labile; is heat resistant at 56 C.; is not adsorbed by barium sulfate, aluminum hydroxide, or other alkaline-earth adsorbents; is active in the presence of platelets; is precipitated from plasma with fibrinogen in salt fractionation but dissociated by heat denaturation of the fibrinogen.

Persistent bleeding, prolonged clotting time, and poor prothrombin consumption may be corrected by fresh blood or plasma, fraction I, barium sulfate–adsorbed plasma, 33 per cent ammonium sulfate fraction, and plasma thromboplastin component–deficient plasma. Clinically, transfusions of whole fresh blood, fraction I, containing antihemophilic globulin, 200 to 600 mg., or fresh, frozen, or lyophilized plasma are administered at eight-hour intervals. Whole blood not only provides antihemophilic globulin and expands blood volume, but also restores red blood cells lost by hemorrhage. Small transfusions at frequent intervals are indicated because antihemophilic globulin tends to disappear rapidly from the circulation. One ml. blood equals 2 mg. fraction I. Transfusions of fresh serum obtained from single donor blood must be utilized within the hour because of rapid conversion of thrombin into metathrombin.

A hemophilic person may become refractory to blood, plasma, or globulin, producing neutralizing antibodies. Fresh frozen plasma loses its antihemophilic property slowly. But it may be used for months after specific preparation for the hemophilic patient without danger of sensitization to erythrocyte antigens. Fraction I must be prepared from fresh plasma, preferably nonpooled plasma, because of the danger of transmitting serum hepatitis and stimulating the development of circulating anticoagulants. Even repeated infusions of plasma or blood will increase anticoagulants associated with the plasma pseudoglobulin fraction, which neutralize the antihemophilic globulin effect through antithromboplastic activity. ACTH will depress such anticoagulant activity temporarily and improve the effect of fresh plasma or blood. Hemophilic bleeding aggravated by loss of vascular tone, contractibility, and resistance is corrected intravenously by antihemophilic globulin and platelets and locally by natural hemostatic agents such as fresh human serum, freshly cut meat and placental tissue or by synthetic preparations such as fibrin foam saturated with tropical thrombin, after removing the soft clots. But hemostatics must be kept ice cold to contract affected vessels.

Plasma thromboplastin component deficiency characterizes sex-linked recessive hemophilia B in the male, which occurs in 15 per cent of the entire group of hemophilic syndromes. Bleeding is most severe in plasma thromboplastin component heterozygotes. Manifestations, course, and prognosis of the condition parallel those of hemophilia A in both mild and severe forms. Prolonged bleeding from infancy, prolonged clotting time, and poor prothrombin consumption may be corrected by fresh blood or plasma, frozen or lyophilized stored plasma or serum, fraction IV, 40 to 50 per cent ammonium sulfate plasma fraction, and true hemophilic plasma, but not by antihemophilic globulin. Fraction IV provides half the plasma thromboplastin component potency of plasma. The thromboplastic generation test differentiates this condition from antihemophilic globulin deficiency, i.e., hemophilia B from true hemophilia. Biggs'[4, 5] thromboplastin generation test is based on the fact that blood can generate a powerful thromboplastin capable of clotting plasma in 10 seconds. The factors necessary for the production of thromboplastin are platelets, plasma thromboplastin component, and calcium. Citrated plasma treated by aluminum peroxide provides antihemophilic globulin and serum and plasma thromboplastin component.

Plasma thromboplastin component is one of the five clotting factors essential for thromboplastin generation. It is concentrated in fractions III and IV_1, is not consumed during clotting, is relatively stable in serum as well as in plasma, is adsorbed by Seitz filtration through barium sulfate, aluminum hydroxide, and tribasic calcium phosphate from oxalated plasma, and is eluted from the adsorbent by sodium citrate. It is present in the 40 to 50 per cent saturated ammonium sulfate fraction of normal plasma but absent in the 0 to 33 per cent saturated fraction containing antihemophilic globulin and in fraction I. The accelerator is heat labile but stable at refrigeration temperatures and resistant to inactivation by *p*H changes. A potent concentrate may be prepared from normal serum by barium sulfate adsorption of acid-inactive serum, since plasma thromboplastin component is associated with the globulin fraction of plasma and serum. When added to plasma thromboplastin component–deficient plasma, this concentrate restores the defective prothrombin utilization to normal.

Plasma thromboplastin antecedent deficiency characterizes hemophilia C, with mild bleeding manifestations. It occurs in both sexes transmitted by an autosomal dominant gene of high penetrance and variable expressivity. The blood shows slightly prolonged clotting time and poor prothrombin consumption, which is corrected by fresh blood or plasma, stored plasma or serum, barium sulfate–adsorbed normal plasma, citrate eluate of the barium sulfate adsorbate, and hemophilic and plasma thromboplastin component–deficient plasma. Hemophilic disorders can readily be distinguished by simple therapeutic tests. The clotting defect in true hemophilia is corrected by normal plasma adsorbed with barium sulfate but not by normal serum; plasma thromboplastin component deficiency, by normal serum but not by barium sulfate–adsorbed plasma; plasma thromboplastin antecedent deficiency, by both normal serum and plasma adsorbed with barium sulfate.

Plasma thromboplastin component deficiency (hemophilia D) is present in both normal plasma and serum as a heat-labile and storage-stable factor. This deficiency induces severe epistaxis and persistent bleeding after marked trauma or surgical intervention. The clotting time is prolonged, prothrombin consumption decreased, and thromboplastin generation retarded. Kugelmass[24] found that the blood of persons with this condition and that of plasma thromboplastin antecedent deficiency are mutually corrective.

Hageman factor deficiency is a hereditary defect in the clotting mechanism discernible only in vitro, since the affected child presents no hemorrhagic tendency. The Hageman factor, which is transmitted by an autosomal gene, is essential for thromboplastin formation in antihemophilic globulin and plasma thromboplastin component and antecedent deficiencies. The clotting time is found to be prolonged on routine tests without clinical manifestation of hemorrhagic disease.

PROTHROMBIN COMPLEX DEFICIENCIES

Congenital hypoprothrombinemia due to deficiency of prothrombin A or B may arise as an inborn error of metabolism from defective protein synthesis in the liver. Absence of prothrombin A is shown by a prolonged prothrombin time when the

other two components are present. Absence of prothrombin B is shown by failure of the prothrombin time to return completely to normal on addition of an equal volume of normal plasma. The defect in neonatal prothrombin activity may be associated with serum prothrombin conversion accelerator deficiency, both depending on a transient deficiency in available vitamin K.

Each defect causes spontaneous, traumatic, or operatively induced bleeding from the gums, nose, vagina, and rectum and into the skin and internal organs. The condition may be alleviated not with water-soluble vitamin K but with vitamin K_1 oxide, 0.5 to 1 Gm. intravenously. Hemorrhage may be arrested by repeated transfusions of fresh whole blood or fresh citrated plasma, the effects lasting for 6 to 24 hours because of the continuous utilization of borrowed prothrombin during hemorrhage, checked by prothrombin time determinations.

Neonatal hypoprothrombinemia may arise in intrauterine life if the mother's diet is inadequate, if vitamin K is not given to the mother a day before delivery or in the neonatal diet during the first days of life, if there is immaturity of neonatal liver function, or if there is absence of intestinal flora that help form prothrombin. Most normal newborn infants reveal a prolonged one-stage prothrombin time within a few hours after birth. It reaches maximum prolongation within three days but gradually attains normal levels within a week. Kugelmass[24] found that the defect in neonatal prothrombin activity is due to deficiencies in both prothrombin and serum prothrombin conversion induced by transient vitamin K deficiency. Spontaneous bleeding between the second and sixth days of life may occur from the gastrointestinal tract, into the skin and brain, or from any site if the prothrombin level falls below 10 per cent of the normal. The low prothrombin activity is not influenced by vitamin K therapy of the mother ante partum but by vitamin K treatment of the newborn infant. Transitory hypoprothrombinemia may be prevented by oral or parenteral administration of 5 mg. of synthetic vitamin K to the mother for several days before delivery, especially in maternal toxemia or in premature or difficult labor. This therapy may prevent intracranial hemorrhage in the newborn infant. Spontaneous bleeding can be alleviated by intramuscular injection of 2.5 mg. of vitamin K at birth to raise plasma prothrombin in three hours or, more rapidly, by transfusing with fresh Rh-negative blood.

Nutritional hypoprothrombinemia occurs with or without hemorrhagic manifestations, the body becoming susceptible to easy bruising, epistaxis, needle puncture hematoma, or dental bleeding. Prothrombin is synthesized by the healthy liver if fat-soluble vitamin K is absorbed from the bowel. Vitamin K_1 is fat soluble when derived from hog's liver, soybeans, alfalfa, or green leaves or when synthesized in the bowel by bacterial action. An inadequate diet or intestinal sterilization with antibiotics may depress blood prothrombin concentration. Mild hypoprothrombinemia may be corrected by 2 mg. daily of water-soluble vitamin K preparations if fat absorption is poor. Severe deficiency requires 5 mg. of parenteral fat-soluble vitamin K_1 or its oxide, each of which is superior to water-soluble synthetic preparations. Besides, the latter can produce hemolysis of red cells containing low glutathione levels and cause hyperbilirubinemia and kernicterus in premature infants.

Gastrointestinal hypoprothrombinemia is due to defective absorption of fat-

soluble vitamin K. Fat absorption is impaired in celiac disease, sprue, short-circuiting operations, regional ileitis, intestinal lipodystrophy, and bowel obstruction. Bile salts fail to enter the intestine in obstructive jaundice or biliary fistula. Faulty absorption also occurs in hyperperistalsis of chronic dysentery and ulcerative colitis. Water-soluble vitamin K, oral or parenteral, is given to patients with intestinal disorders. Fat-soluble vitamin K is given with bile salts to assure absorption, using plasma prothrombin determinations as guides to treatment. Vitamin K is also prescribed for hypoprothrombinemias below 75 per cent of normal preoperatively to prevent further depression to 15 per cent of normal, the critical level for bleeding.

Hepatic hypoprothrombinemia is due to failure of prothrombin synthesis by the liver in hepatic disorders even though fat-soluble vitamin K is abundantly absorbed. Hemorrhage from mucous membranes into the skin and internal organs occurs in postanesthetic liver injury; acute yellow atrophy; Laënnec's cirrhosis; infiltration with malignant or leukemic cells; chemical poisoning with phosphorus, chloroform, or arsenic; and traumatic or surgical shock. Bleeding may be arrested with large transfusions of fresh blood or 1000 ml. of plasma with due consideration to the risk of infectious hepatitis from pooled plasma. Intramuscular vitamin K is ineffective if there is severe liver dysfunction; hence vitamin K_2 is given intravenously in the presence of jaundice or possible vitamin K deficiency.

In chemical hypoprothrombinemia due to anti-vitamin K activity by bihydroxycoumarin, salicylates, quinine, Tromexan, phenyl indandione, etc., the formation of prothrombin is suppressed in the liver without any direct action on prothrombin. Overdosage of bishydroxycoumarin leads to severe hemorrhages from the skin and mouth and even into the brain. Salicylates may reduce plasma prothrombin sufficiently to cause bleeding, since salicylic acid is a degradation product of bishydroxycoumarin. Normal prothrombin levels may be promptly restored by discontinuance of the drug and administration of vitamin K and supportive transfusions until the anticoagulant action has been neutralized. Emergency transfusion of fresh whole blood supplemented by 500 to 1000 ml. of fresh plasma controls bleeding for about five hours, since the prothrombin supplied by blood and plasma is rapidly diluted in the circulation. A simple transfusion will promptly raise the prothrombin level to 30 per cent, while vitamin K will take several hours to increase the prothrombin; hence massive doses of vitamin K are offered after transfusion.

Prothrombin Accessory Factor Deficiency. Accelerator globulin or labile factor activity is normally present in the newborn infant. Its deficiency may be congenital or acquired. Serum prothrombin conversion activity or stable factor activity is also present in the newborn infant and is dependent on vitamin K for its synthesis, comparable to prothrombin. Its deficiency may be congenital or acquired.

Accelerator globulin deficiency occurs in circulating blood as inactive plasma accelerator globulin readily transformed by thrombin into active serum accelerator globulin during blood clotting. Small amounts of thrombin catalyze the formation of active accelerator globulin, but large amounts reverse the reaction reproducing inactive accelerator globulin. The globulin is formed for the first and second stages of clotting, transforming prothromboplastin into thromboplastin, stoichiometrically, and accelerating prothrombin into thrombin in the presence of Ca^{++} and thrombo-

plastin, catalytically. Prothrombin prepared by salt precipitation forms thrombin rapidly in the presence of Ca^{++} and thromboplastin. But prothrombin prepared by adsorption with aluminum hydroxide and subsequent elution forms thrombin very slowly.

The rate of conversion can be accelerated by addition of a small amount of the plasma from which the prothrombin has been adsorbed. Owren[28] found that water-soluble accelerator globulin was destroyed by heating to 56 C. for half an hour, by increasing the *p*H to 10.5, by standing at room temperature or at +5 C. for 48 hours, or by storage with oxalate but not with citrate ions. Chemically, accelerator globulin is similar to prothrombin but is not separated from plasma by barium sulfate or tricalcium phosphate or 50 per cent asbestos filter, hence the ease of preparing concentrates in fractions II and III with β-lipoproteins 150 times that of plasma. Accelerator globulin can be precipitated by 45 per cent ammonium sulfate, adsorbed at *p*H 5.4 on magnesium hydroxide, redissolved with carbon dioxide, and frozen without loss of activity. But the accelerator is extremely labile in oxalated and citrated blood and is destroyed within a few days in stored bank blood.

Accelerator globulin deficiency may be congenital, transmitted as an autosomal dominant with reduced penetration. The bleeding into the skin and muscles simulates the hypoprothrombinemias characterized by prolonged bleeding tendency from infancy, prolonged clotting time, poor prothrombin consumption, prolonged prothrombin time, abnormal plasma thromboplastin generation, and normal serum thromboplastin generation. Acquired accelerator globulin deficiency shows low levels of accelerator globulin activity in severe hepatic disease, acute leukemia, postoperative states, irradiation injury, isotope administration, and late stages of cancer. Clinically, the bleeding may be controlled by fresh whole or fresh citrated plasma transfusions repeated at 24-hour intervals, the survival period of accelerator globulin administered intravenously. It is usually effective for several days owing to the relatively small requirement of accelerator globulin as determined by the rapid return of the elevated prothrombin time to normal.

Serum prothrombin conversion factor deficiency accelerates the conversion of prothromboplastin into thromboplastin by accelerator globulin and prothrombin into thrombin by thromboplastin and calcium. Formed in the liver in the presence of vitamin K, serum prothrombin conversion accelerator is distinct from accelerator globulin and cannot replace it in the clotting system. It is readily adsorbed by barium sulfate and aluminum hydroxide and eluted with citrate-like prothrombin. Serum prothrombin conversion accelerator, the stable factor, retains its activity for four days at a temperature of 25 to 37 C. in stored serum. Duckert et al[6] isolated this factor by adsorption with barium sulfate, elution with sodium citrate, and precipitation with ammonium sulfate. Lewis et al[25] separated serum prothrombin conversion accelerator from prothrombin chromatographically by precipitation at various *p*H's. The purified fraction of Ferguson et al[7] contains carbohydrate but no cholesterol.

Singly both serum prothrombin conversion accelerator and platelets are devoid of thromboplastic activity, but together they exhibit great thromboplastic activity, quantitatively comparable to that of brain or lung. This activity can be increased

by preincubation of platelets with serum prothrombin conversion accelerator to convert prothrombin to thrombin without calcium. Alexander et al[2] demonstrated its absence in a human hemorrhagic disorder despite normalcy of all other clotting components. Goldstein et al[10] observed that plasma prothrombin devoid of this factor is only very slowly converted to thrombin by thromboplastin and calcium. Serum prothrombin conversion accelerator arises from a relatively inert plasma precursor, pro-serum prothrombin conversion accelerator, during coagulation, evolving in relation to the amount and velocity of prothrombin conversion. Storage by refrigeration slowly transforms the precursor into serum prothrombin conversion accelerator, and it remains unaltered for four days at 25 to 37 C. in stored serum.

Serum prothrombin conversion accelerator deficiency is transmitted as an autosomal dominant by either sex, develops occasionally in the neonatal period or in advanced liver disease, and is deliberately induced by administration of bishydroxycoumarin, Tromexan, Treburon, Paritol, and other anticoagulants in incipient or established thrombosis. The blood in serum prothrombin conversion accelerator deficiency shows normal clotting time, but elevated prothrombin time, corrected in vitro by addition of purified serum prothrombin conversion accelerator and temporarily in vivo by intravenous administration of human serum, bank blood, or citrated plasma until the prolonged prothrombin time becomes normal. Crude serum prothrombin conversion accelerator contains two factors, serum prothrombin conversion accelerator and another accelerator, which Koller et al[14] call factor X. The Stuart-Prower factor, closely related in serum prothrombin conversion accelerator activity, is inherited as an incompletely recessive characteristic of high penetration. Refined serum prothrombin conversion accelerator loses all power to correct the coagulation defect in deficiency of this accelerator.

FIBRINOGEN DEFICIENCY

Congenital Hypofibrinogenemia. Complete absence of fibrinogen is inherited by children of either sex derived from some marriages of first cousins. Henderson et al[12] considered afibrinogenemia a recessive non-sex-linked characteristic, attributed to the lack of a gene that carries fibrinogen. Afibrinogenemia thus constitutes a homozygous state, and fibrinogenopenia constitutes a heterozygous state of fibrinogen deficiency. The newborn infant bleeds profusely from the umbilicus; the infant, after eruption of the milk teeth; and the child, after slight trauma. Once the bleeding starts, it continues for hours or days. When the bleeding ceases, a long time seems to pass before another attack. In congenital afibrinogenemia, the blood does not coagulate. Nevertheless, only mild bleeding occurs, except after trauma. This emphasizes the relative unimportance of major defects in the clotting mechanism provided the platelet and vascular components are normal.

Shortly after exposure of afibrinogenemic blood to glass, Alexander et al[3] observed morphological changes in the platelets with rapid agglutination, rapid decline of antihemophilic globulin, appearance of serum prothrombin conversion accelerator, and consumption of accelerator globulin before detectable amounts of prothrombin disappeared. Fibrinogenopenia is probably more common than is realized, yet it is

not detected because of failure to determine the level of plasma fibrinogen or to observe the few strands of fibrin formed within the normal clotting time. The fine fibrin filament is insufficient to bind the cellular elements into a real clot. An abnormal level of fibrinogen may also be suspected from a retarded erythrocyte sedimentation rate—the less the fibrinogen, the slower the rate.

Fibrinogen deficiency is confirmed by the inability of the blood to clot after the addition of thrombin and thromboplastin and by lack of formation of a fibrinogen precipitate on warming the patient's plasma to 60 C. or adding 25 per cent saturated ammonium sulfate or 50 per cent sodium chloride. The prothrombin time of undiluted plasma is infinite, but normal on addition of fibrinogen; protiirombin utilization during clotting is normal; rate of thrombin formation, normal; clotting factors involved in the thromboplastin and thrombin formation, normal; platelet count, slightly reduced; bleeding time, prolonged; tourniquet test, positive; whole blood clotting time, greatly reduced; the clot formed, friable; clot retraction, prompt; and the fibrinogen level, 0.01 to 0.5 Gm./100 ml.

Hemorrhages may be controlled by transfusions of whole blood, fresh plasma, or preferably fraction I, which provides 60 per cent fibrinogen. Plasma fibrinogen may be elevated 10 mg./100 ml. by adding intravenously 0.25 Gm. fibrinogen per 100 ml. The fibrinogen level must be maintained above the critical level for bleeding by administration of 10 units of plasma or the equivalent in fibrinogen. Injection of 200 mg. at the onset of bleeding maintains blood fibrinogen at the normal level of 200 mg./100 ml. Since the child's blood level of replaced fibrinogen diminishes partly within five days and completely within 30 days to less than 60 mg./100 ml., the critical level for bleeding, the same dose of plasma fraction I is injected at monthly intervals. This procedure enabled Kugelmass[28] to maintain affected twins free from hemorrhagic manifestations throughout early childhood.

Acquired Hypofibrinogenemia. Symptomatic hypofibrinogenemia may be due to defective fibrinogen formation, intravascular clotting, or fibrinogen destruction by fibrinolysis. The level of plasma fibrinogen is an index of liver function. Fibrinogenopenia occurs in deficiency diseases, e.g., scurvy, pellagra, and pernicious anemia; in bone marrow diseases, especially myelogenous leukemia and polycythemia; in liver diseases where extensive injury has reduced fibrinogen formation as a terminal event; in severe infectious diseases, such as scarlet fever, pneumonia, tuberculosis, and brucellosis, which destroy liver structure and increase circulating fibrinolysin; in pregnancy when there occurs amniotic fluid infusion, premature separation of the placenta, or intrauterine fetal death, producing intravascular defibrination; or in the course of massive transfusions of bank blood devoid of fibrinogen. Bleeding is controlled by transfusion of fresh whole blood, fresh plasma, or fraction I to raise plasma fibrinogen above 100 mg./100 ml. The survival studies of Gitlin et al[9] with chemical tagging revealed that half the administered fibrinogen disappeared within 48 hours and the rest according to a slow logarithmic curve, indicating a half life of five days.

FIBRINOLYTIC EXCESS

Fibrinolytic Purpura. The plasma proteolytic enzyme profibrinolysin is activated

by fibrinolysokinase normally inhibited by antifibrinolysokinase in tissues. Normal enzyme dissolution of fibrinogen strands occurs in fibrinogen metabolism and after tissue repair; mild plasma fibrinolysis, after exercise, anxiety, alarm reaction, and epinephrine injection; marked fibrinolysis, after cyanotic congenital heart disease, surgical operation, transfusion reaction, hemolytic crisis, hemorrhagic shock, anaphylactoid reaction, burns, severe injury, liver disease, bacterial infection, leukemia, and malignant neoplasm. The affected blood will clot readily but the clot will disappear in 24 hours if a sterile sample of clotted blood is incubated at body temperature. The degree of fibrinolysis is thus inversely proportional to the time required for the dissolution of the clot.

Excessive activation of fibrinolysin induces acute or chronic severe generalized bleeding, which is difficult to control because of marked reduction in fibrinogen, prothrombin, and prothrombin conversion factors—the protein moieties involved in blood coagulation. Slow lysis induces moderate bleeding unless other clotting disorders accompany fibrinolysis. Rapid lysis of the clot within 30 to 60 minutes produces severe bleeding. Indeed, the activity of the enzyme is a direct function of the time required for the lysis of the test clot at 37 C. Faulty activation of fibrinolysin is corrected by ACTH or cortisone therapy. Destroyed clotting components are replaced by concentrated fibrinogen in fraction I, by large amounts of plasma, and by human antifibrinolysin.

CIRCULATING ANTICOAGULANT EXCESS

Hyperglobulinemia accompanied by circulating anticoagulants occurs in infectious diseases, endocarditis, liver disorders, malignancies, agranulocytosis, pancytopenia, and hemophilia. There is considerable increase in γ-globulin and in the 7-component in the ultracentrifuge. The excessive plasma proteins, normal or abnormal, bind the clotting components, interfere with thromboplastin formation, and inhibit thrombin generation. The increase of mast cells in the bone marrow indicates increased heparin activity in the circulation.

Antithromboplastins are γ-globulins resistant to heat at 65 C. and to storage, are nondialyzable, nonextractable with ether, and nonadsorbed by gels. If the anticoagulant prevents thromboplastin formation, there is marked impairment in prothrombin consumption. If the anticoagulant reveals heparin-like activity, plasma prothrombin activity diminishes, prothrombin utilization during clotting is impaired, and antithrombin content elevated. Anticoagulants inhibiting thromboplastin activity occur in chronic glomerulonephritis, lupus erythematosus, polyarteritis nodosa, pemphigus, tuberculosis, and in hemophilic persons after repeated transfusions.

The anticoagulant in hemophilia is directed specifically against antihemophilic globulin, which is inhibited in vivo and precipitated in vitro. James et al[12] found that D^u (F^y)-negative patients transfused with D^u (F^y)-positive blood may develop circulating anticoagulants. Frick[8] reported the development of an antithromboplastin during a first pregnancy, which reappeared during the second pregnancy. Circulating anticoagulants also develop in persons with immunological disturbances,

especially in the presence of auto-iso-red cell agglutination and a positive Coombs' test. Hemorrhagic diathesis from circulating anticoagulants in the female simulates hemophilic syndromes in heredofamilial plasma defects, hemophilic shock in transfusion reactions, pregnancy disorders, prostatic cancer, and excessive roentgen ray irradiation. The profuse and persistent bleeding cannot be arrested by massive transfusion.

Hyperheparinemia is observed in leukemia, aplastic anemia, lymphosarcoma, Hodgkin's disease, nitrogen mustard therapy, and after ionizing irradiation. The heparin-like substance is identified by protamine titration. Other anticoagulants, such as hirudin from leech extract, produce an antithrombin effect. The clotting and bleeding times are prolonged and the platelets diminished. The bleeding may be controlled with intravenous injections of protamine sulfate, 0.3 mg./Kg. of body weight in 50 ml. of saline solution every 24 hours, or the less toxic toluidine blue dye, 2.5 mg./Kg. of body weight daily. Platelets can be provided by repeated fresh whole blood transfusions until recovery. Overdosage of heparin therapy in thrombosis may be neutralized by injecting intramuscularly 1 mg. of protamine per Kg. of body weight in 200 ml. saline solution over a period of 10 minutes. Protamine combines with heparin in the ratio of 2:1 and inactivates the anticoagulating properties within several minutes.

VASCULAR PURPURAS

Congenital Capillary Defects. Hereditary telangiectasia may be transmitted by either parent to both sexes but is not manifested until puberty. Repeated bleeding occurs from multiple dilations of capillaries and venules in the skin and mucous membranes. The bleeding time is prolonged in the affected area but remains normal in the blood of nonaffected capillaries. Epistaxis may be arrested with tampons of thrombin or fibrin foam and bleeding points cauterized with a chromic acid bead, electrocoagulation, or submucous injection of 5 per cent quinine and urethan. Capillary permeability may be decreased by hesperidin or rutin, 100 mg., and ascorbic acid, 250 mg. daily.

Cutis hyperelastica is an inherited defect in connective tissue that leads to an overproduction of elastic tissue. Cutaneous vessels lack connective tissue support and bleed profusely on slight trauma. The skin is hyperelastic and the joints hyperextensible. There is extreme laxity of the skin and joints at birth and fragility of the skin and blood vessels when the infant begins to walk, but there is no tendency to excessive bleeding from wounds.

Pulmonary hemosiderosis, due to increased fragility of lung capillaries, is characterized by recurrent attacks of severe hemoptysis in children. There are progressive dyspnea, cyanosis, and pulmonary edema. The blood shows marked hypochromic anemia, bilirubinemia, and reticulocytosis. The lungs are filled with iron deposits in the alveolar cells, limiting life to several years after the onset.

Congenital Platelet Defects. In this condition, the platelets are normal in number but exhibit morphological abnormalities in size, appearance, and staining. Serotonin deficiency causes prolonged bleeding time; retractoenzyme deficiency, impaired clot retraction; factor I deficiency, prolonged plasma prothrombin time; factor de-

ficiency, poor fibrinogen conversion; thromboplastic deficiency, poor prothrombin utilization during clotting.

Hereditary thrombocytoasthenia (Glanzmann's syndrome) is a qualitative platelet defect accompanied by constitutional fragility of the blood vessels. The blood of both male and female offspring of affected families shows relatively normal numbers of small round platelets with impaired adhesiveness and agglutinability. The platelets dissociate too slowly for effective hemostasis, resulting in prolonged bleeding time and poor clot retraction, but clotting time and prothrombin consumption are normal. Excessive bleeding, easy bruising, abnormal contractility of nail bed capillaries after injury, and recurrent purpura respond to thrombin-fibrin foam applications. Severe hemorrhagic episodes can be controlled with fresh whole blood transfusions from polycythemic donors. The natural tendency to spontaneous improvement at maturity precludes ineffective splenectomy.

Constitutional thrombopathy (von Willebrand's syndrome) involves recurrent spontaneous hemorrhage as an heredofamilial tendency, transmitted by either parent to both sexes. The blood shows prolonged bleeding time and positive tourniquet test, but normal clotting time, efficient clot retraction, and adequate platelets that are bizarre in form and inefficient in function. Persistence of bleeding simulates hemophilia, especially with a variable decrease in antihemophilic globulin, hence the difficulty of diagnosis in the male. Accessible bleeding may be controlled with topical thrombin fibrin foam; inaccessible bleeding, with fresh whole blood transfusions; and capillary endothelium improved with hesperidin, 100 mg., and vitamin C, 500 mg. daily.

Chemical Purpura. Ascorbic acid deficiency or scurvy, latent or manifest, halts the laying down of intracellular collagen in the vascular endothelium. Infants develop swollen, bleeding gums, painful subperiosteal hemorrhages, and hematuria. Adults bleed into the orbital fossae, mucous membranes, and skin. All clotting tests are normal but capillary fragility is markedly increased. There may be low plasma and white cell ascorbic acid levels in severe scurvy. Hemorrhages are cleared with 250 mg. of ascorbic acid and capillary permeability is decreased with 100 mg. of hesperidin, daily.

Drug poisoning induces purpura by toxic inhibition or by antigen-antibody reaction of the endothelial cellular enzymes essential for the maintenance of the vessel wall. But snake venom injures the endothelial lining of the capillaries and venules.

Allergic Purpura. Bleeding into the skin, joints, and viscera is associated with allergic manifestations. The exciting agent may be infection, food, or cold causing an antigen-antibody reaction in the vascular endothelium of some blood vessels with consequent alteration in the vascular permeability. The various manifestations arise from extravasations of blood plasma and formed elements. A protein antigen may yield to desensitization; otherwise ACTH and cortisone are effective. Purpura simplex is a hereditary tendency to easy bruising found especially in infants and adolescent girls of allergic families. Symmetrical purpuric spots appear about the hair follicles in the upper and lower extremities, especially after an attack of headache, fever, and malaise. If severe, the bleeding may be intramuscular, subperiosteal, or visceral, accompanied by allergic skin lesions. Henoch's purpura begins with

vomiting, fever, diarrhea, abdominal distention, and colic before any purpuric eruptions develop. The allergic gastrointestinal disturbance is produced by an urticarial serohemorrhagic effusion into the intestinal wall, accompanied by ecchymoses, hematemesis, melena, or hematuria. Schoenlein's purpura develops as a migratory disturbance produced by periarticular effusions. The affected joints become purpuric, painful, swollen, tender, hot, and red, the face and eyelids edematous, and the trunk urticarial.

Infectious Purpuras. Hemorrhagic infections cause capillary injury by toxins in scarlet fever, measles, pneumonia, diphtheria, acute and chronic glomerulonephritis, typhus, smallpox, spotted fever, and meningococcic meningitis. Bacterial emboli produce purpura in subacute bacterial endocarditis, typhoid fever, and meningococcic septicemia, the organism often being demonstrable in the purpuric skin lesions.

Purpura fulminans is characterized by large symmetrical ecchymoses over the skin surfaces but never from mucous membranes or from internal viscera. The blood platelets are normal, accelerator globulin levels and capillary resistance diminished. The centers of vascular innervation in the spinal cord are involved. The child usually succumbs within four days, although purpura complicating scarlet fever may be relieved by daily intravenous infusions of the amino acid methionine, 3 Gm. in 500 ml. of saline solution.

Waterhouse-Friderichsen syndrome is precipitated by bilateral hemorrhage into the adrenal glands, which produces cyanosis, shock, and fever. Respirations become rapid and labored and the child sinks into a deep coma. Petechial and purpuric spots appear over the entire body and coalesce into ecchymoses. In the newborn infant the adrenal hemorrhage is induced by birth trauma. In the infant and older child, the condition is precipitated by infection—meningococcic, streptococcic, pneumococcic, or diphtheritic. Infection is combatted with sulfonamides and antibiotics, intravenous infusions of plasma and fluid reinforced with adrenocortical extract, 10 ml., vitamin K for the newborn infant, and vitamin C for the older child.

Mechanical Purpura. Capillary bleeding may be induced in a normal person in any region of the body subjected to sudden increase in venous pressure. Whooping cough may produce bleeding from the conjunctivas, nose, eyelids, and bronchi. Rheumatic heart disease may cause epistaxis or petechial hemorrhages in the extremities. Convulsions may produce purpura in the head and upper extremities from increased pressure within the blood vessels. Uremia may cause cerebral, retinal, and intestinal hemorrhage from the concurrent hypertension. Leukemia may cause bleeding by infiltration of the walls of the blood vessels. Extremes of heat or cold may cause exposed areas to bleed. Chronic anoxemia of a part of the body may lead to localized petechial hemorrhage. Trauma may induce vascular purpura in the affected region. Prolonged standing may cause orthostatic purpura in the lower extremities if the capillaries are defective.

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Course in Rehabilitation Care of the Chronically Ill Patient

A one-week course for physicians, devoted to the rehabilitation care of the chronically ill patient, will be held Nov. 14–18, 1960, under the auspices of the Department of Physical Medicine and Rehabilitation, New York Medical College-Metropolitan Hospital Center. The course will offer a review of the principles and techniques in the medical care of the chronically ill to meet the needs of the clinician, medical administrator, and public health physician. Course content will include: physiology and pathology of chronic diseases, nutrition and dental care, management of bedridden and incontinent patients, home care programming, community needs and resources, public health aspects, self-care activities, prosthetic devices, and psychological and social aspects.

The tuition fee is $150.00. Traineeships for tuition, maintenance, and travel are available through funds provided by the U. S. Office of Vocational Rehabilitation. Applications for the course and traineeships can be obtained directly from Dr. Jerome S. Tobis, Chairman, Department of Physical Medicine and Rehabilitation, New York Medical College, 1 East 105th Street, New York City 29.

Thromboelastography in Hemorrhagic Disorders

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A general survey of thromboelastography in hemorrhagic disorders implies some preliminary considerations on the limits of this subject. As a rule, a hemorrhagic disorder may be due to an impairment of the blood coagulation mechanisms and factors and/or to a lesion of the vascular walls, resulting in an insufficient hemostasis.[1] Such a distinction clearly indicates that not all hemorrhagic disorders are characterized by pathological alterations of the diagnostic tests that are used for the clinical study of blood coagulation, but in only some of these disorders is a coagulation defect detectable. It should be emphasized, from the very beginning, that a coagulation defect is not necessarily accompanied by a bleeding symptomatology: in several cases, additional factors may be operating in conjunction with the coagulation defect to cause hemorrhages. In some conditions (e.g., Hageman phenomenon), a definite coagulation defect is always and completely asymptomatic as far as hemorrhages are concerned.

Thromboelastography, as a method for the study of blood coagulation, is obviously suitable only for investigating those hemorrhagic disorders that are accompanied by a coagulation defect. As will be seen, thromboelastography cannot replace all other methods—old and new—for the study of blood coagulation, but among the coagulation defects are some that are particularly suitable for a thromboelastographic study, insofar as they show typical characteristic alterations of the thromboelastographic patterns.

According to the most accepted interpretation, thromboelastography makes it possible to measure and record automatically the modifications of the following physical properties of the clot during its formation: adhesiveness, resistance to traction, and elasticity (within certain limits). Recently there have been suggestions to rename the method thrombodynamography[2] or coagulography.[3, 4] The term "thromboelastography," which was first suggested by Hartert[5–9] in his pioneer and fundamental work, is still widely used in coagulation studies as well as in monographs on thromboelastography,[10–15] which are recommended to the reader for further data on the basic aspects of thromboelastography.

The components of a thromboelastogram are well known (fig. 1): the reaction time, the clot formation time, and the maximal amplitude. Such a pattern is obtained under standard conditions, namely, when whole blood as well as oxalated or citrated plasma is recalcified in the cuvet of the thromboelastograph.

When a study of fibrinolysis (spontaneous or streptokinase activated) is undertaken, other components should be considered, as shown in figure 2, in addition to the standard components. For practical purposes, the most important component under these conditions is the lysis time.

Several criteria were suggested for a further evaluation of the thromboelastogram and its components. Some value was assigned to the so-called thromboelastographic

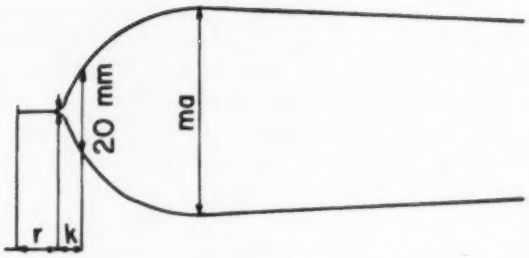

FIG. 1. Scheme of a thromboelastogram. r = reaction time; k = clot formation time; ma = maximal amplitude.

index, which is obtained by dividing reaction time plus clot formation time by maximal amplitude.

As a general rule, a prolongation of reaction and clot formation times as well as a decrease of maximal amplitude is consistent with a hypocoagulability state, while the opposite situation (reduction of reaction and clot formation times and decrease of maximal amplitude) is typical of the hypercoagulability states. In many cases, however, there are various combinations of these findings.

Thromboelastography in the Study of Hemorrhagic Disorders with Coagulation Defects. As noted previously, among the hemorrhagic disorders, only those with coagulation defects can be submitted to a thromboelastographic analysis. Now let us examine in which conditions a pathological alteration of the thromboelastographic pattern can be observed, with particular reference to the hemorrhagic disorders of childhood.

For a better evaluation of the various alterations in the different age groups, a brief remark should be made about the thromboelastographic values in normal children and adult subjects. During the first year of life, a moderate increase of the maximal amplitude values is observed, with a slight reduction of the reaction and clot formation times. There is, namely, an increased coagulability as compared with that in the normal adult. During the second year of life, there is a progressive reduction of such a state, while in the subsequent years the normal adult values are

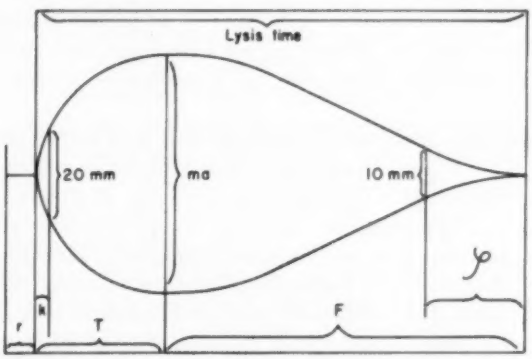

FIG. 2 Scheme of a thromboelastogram with fibrinolytic activity; the lysis time is the most important component for practical purposes.

gradually reached.[16, 17] Interestingly enough, comparative researches on the thromboelastographic values of various animals have shown that significant differences are demonstrable also between young and adult animals.[18] In immature infants, there is instead a hypocoagulability state, with slight prolongation of reaction and clot formation times and a significant decrease of maximal amplitude. Within 60 days after birth, these findings in immature infants are completely normalized.[20]

Our present knowledge of thromboelastography and the actual value of this technique does not permit us to attempt any classification on a thromboelastographic basis, nor to follow strictly the physiopathological classifications that are generally used in coagulation studies, when other tests are employed. However, it is possible to analyze the thromboelastographic data by considering the following: general significance of the thromboelastographic components, typical thromboelastographic patterns in coagulation disorders, and special procedures for a further evaluation of the thromboelastographic data.

General Significance of the Thromboelastographic Components. It is generally assumed that the reaction time of the thromboelastogram represents an approximate equivalent of the recalcification time in vitro. This assumption is not completely nor always valid.

As a rule, the reaction time depends on at least three factors: the rate and amount of fibrin formation, the adhesiveness of fibrin to the walls of the cuvet, and the resistance of fibrin to traction. When adhesiveness and resistance of fibrin are normal, the rate and amount of fibrin formation chiefly influence the reaction time, which can then be considered as an equivalent of the recalcification time. This is the case in hemophilic syndromes and fibrinogenopenia, in which the rate and the amount of fibrin formation, respectively, are impaired.

If fibrin does not adhere or resist traction normally, there is a prolongation of reaction time, which is relatively longer than the recalcification time. This happens when a platelet impairment takes place due to reduction of platelet count and/or of platelet functional activities.

The clot formation time can be analyzed on the basis of similar considerations. There might be a prolongation of the clot formation time either in the presence of a delayed or reduced fibrin formation or because of an impaired adhesiveness and resistance of the fibrin threads. Therefore, we have again two conditions in which the clot formation time is prolonged, i.e., the hemophilic syndromes and the platelet diseases.

As far as the maximal amplitude is concerned, it is well known that several factors may modify it. This is particularly true when hemorrhagic disorders with coagulation defects are considered. The most frequent cause of a decreased maximal amplitude, resulting in a hypocoagulability state, is represented by platelet deficiency, due to decrease of platelet count and/or platelet functional activities.

It was assumed that thrombin formation might also influence the maximal amplitude values in the sense that a decreased or delayed thrombin formation would bring about a reduction of these values. Such an interpretation might be applied to the coagulation defects without any primary platelet involvement, such as deficiency of prothrombin and accelerators. However, it is possible that a decreased or delayed

thrombin formation impairs the functional activity of platelets, thus causing a secondary platelet involvement and a decrease of the maximal amplitude. In this respect it should be emphasized that such a hypothetic mechanism is valid only for forming thrombin and not for already formed thrombin, which has, instead, a negative effect on maximal amplitude. Some serum factors may possibly be involved in such a mechanism, as several experimental observations seem to confirm.[21]

Some considerations are feasible also for the thromboelastographic components when spontaneous or streptokinase-activated fibrinolysis takes place. As was noted previously, the most important component is represented in such conditions by the lysis time, which might be considerably reduced when an increased fibrinolytic activity is present, as happens when fibrinolysis is studied in vitro.

There is, however, a difference between the two techniques. The lysis time as observed in vitro indicates the complete dissolution of the fibrin clot, which is no longer visible as such. In the thromboelastographic tracing, the lysis time does not necessarily mean the complete dissolution of the fibrin clot, but only the dissolution of those fibrin threads that cause the adhesiveness and resistance to traction of the fibrin clot. A complete agreement between the two techniques is, therefore, not always demonstrable, although the values are in general comparable.

Typical Thromboelastographic Patterns in Hemorrhagic Disorders with Coagulation Defects. On the basis of the previous considerations, the thromboelastographic characteristics of hemorrhagic disorders with coagulation defects can be grouped into three main types, as follows:

Hemophilic Type. In this type there is a prolongation of the reaction time and of the clot formation time without significant modifications of the maximal amplitude, which might even be increased.

Thrombocytopenic Type. This type is usually characterized by a prolongation of the reaction time and a decrease of the maximal amplitude, with normal values or a slight prolongation of the reaction time.

Fibrinolytic Type. In this type the lysis of the fibrin clot can be demonstrated on the basis of thromboelastographic observation of the lysis time, which cannot be measured under normal conditions.

These three principal types of alterations represent only the general pattern that may be followed, completely or partly, by the various coagulation disorders. The thrombophilic type is obviously not related to hemorrhagic diseases, but some signs of the thrombophilic tendency might occur even in typical coagulation defects. For instance, in hemophilic syndromes, the increase of the maximal amplitude can be interpreted as the consequence of the slow but continuous thrombin formation. In fibrinogenopenias due to intravascular clotting, the hypocoagulability patterns may be accompanied by a shortened reaction time as the only expression of the intravascular thrombin formation.

The three thromboelastographic types are named according to the conditions in which they are most typically observed. There are, however, many other conditions that show these features, at least in part. A brief survey of all these conditions will give an idea of the diagnostic applications of these concepts.

The hemophilic syndromes present, quite frequently, the thromboelastographic

FIG. 3. Some thromboelastograms in hemophilic syndromes: prolongation of the reaction time and of the clot formation time, normal or supernormal values of the maximal amplitude. (From: DE NICOLA, P.: La formazione del coagulo e le sue alterazioni sulla base di nuovi dati sperimentali e clinici, Haematologica *41*:1169, 1956.)

characteristic of the hemophilic type, with a typical proportion between the prolongation of the reaction time and the prolongation of the clot formation time (figs. 3 and 4). Only those hemophilic syndromes that are accompanied by a prolonged whole blood clotting time exhibit detectable modifications of the thromboelastogram. Mild hemophilias, with normal whole blood clotting time, even in the presence of a marked defect of a coagulation factor (factor VIII, antihemophilic globulin or factor; factor IX, plasma thromboplastin component), cannot be recognized by means of thromboelastography.

The hemophilic type is also found in those hemophilia-like syndromes in which there is a prolongation of the whole blood clotting time, as happens in severe, congenital deficiency of prothrombin, factor V, factor VII, factor X (Stuart-Prower). If the deficiency is of slight degree, thromboelastography is usually not able to demonstrate any significant alterations, as is observed in some cases of plasma thromboplastin antecedent deficiency.

The thrombocytopenic type is obviously characteristic of thrombocytopenias, both primary and secondary in nature, with a decrease of platelet count and all other signs of hemostatic impairment due to insufficient platelet functional activity (figs. 5 and 6). A definite proportion between the degree of the thromboelastographic alterations and the platelet count can be demonstrated only under certain experimental conditions. It seems that the functional activities of platelets are reflected in the thromboelastogram, irrespective, within certain limits, of the actual platelet

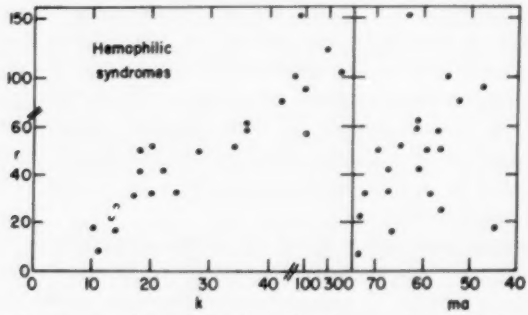

FIG. 4. Correlations between reaction and clot formation times, and reaction time and maximal amplitude, in hemophilic syndromes. There is a fair proportion between reaction and clot formation times.

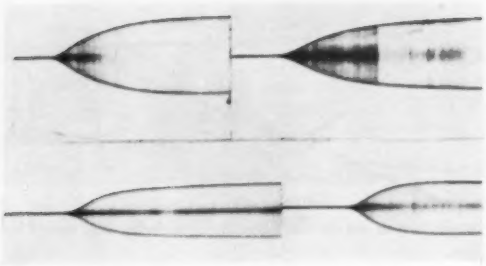

FIG. 5. Some thromboelastograms in thrombocytopenias: moderate prolongation of the reaction time, marked prolongation of the clot formation time, and marked decrease of the maximal amplitude. (From: DE NICOLA, P.: La formazione del coagulo e le sue alterazioni sulla base di nuovi dati sperimentali e clinici, Haematologica *41*:1169, 1956.)

count. This might explain why the thrombocytopenic type is also observed in thrombocytopathies, with normal platelet count, and why a severe defect is often not demonstrable by means of thromboelastography in the presence of a marked thrombocytopenia, probably because the few platelets available still keep their functional activities unaltered.

A wide field of thromboelastographic applications is presented by all those conditions in which intermediate patterns are observed, mostly of moderate degree, but clearly indicating the presence of a coagulation defect. A great variety of combinations occurs in these conditions, depending on the predominance of the hemophilic pattern or of the thrombocytopenic pattern, respectively. As has been already mentioned, a decrease of the maximal amplitude, thus resembling the thrombocytopenic pattern, may be observed also in conditions without any primary platelet involvement. This is particularly true for several acquired hemorrhagic disorders with coagulation defects that do not follow the characteristic patterns of the isolated congenital defects, but reflect a combination of various defects.

Some typical conditions will be mentioned here. A coagulation defect of various degree can be detected by means of thromboelastography in liver diseases, with or without hemorrhagic disorders, thus reflecting the decreased concentration of several plasmatic factors (prothrombin, fibrinogen, factors V, VII, IX, X) and a platelet involvement, which might be partly primary, partly secondary in nature.

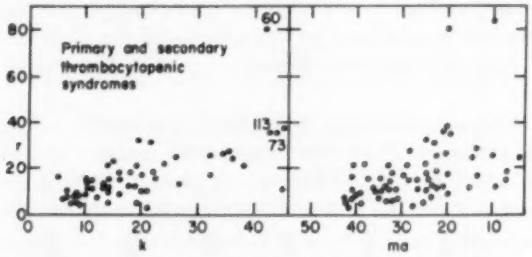

FIG. 6. Correlations between reaction and clot formation times, and reaction time and maximal amplitude, in thrombocytopenic syndromes.

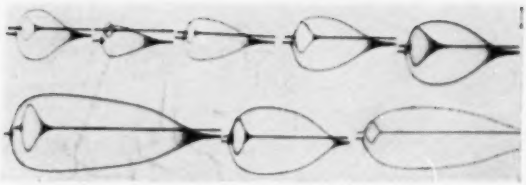

FIG. 7. Examples of streptokinase-activated fibrinolysis in various conditions. Each group of thromboelastograms refers to a single case in which the fibrinolytic activity was tested by means of different concentrations of streptokinase.

In hemorrhagic disease of the newborn infant, the coagulation defect influences the thromboelastographic pattern, through decreased concentration of plasmatic (chiefly, prothrombin, factors VII, IX, and X) and platelet factors, thus causing thromboelastographic alterations of intermediate type. It should be remembered that a severe defect must be present when evident thromboelastographic alterations are demonstrable.

Anticoagulant therapy also results in thromboelastographic modifications, which follow the hemophilic and/or thrombocytopenic pattern, according to the intensity and the nature of the coagulation defect.

The third thromboelastographic pattern that deserves special mention with respect to hemorrhagic disorders is represented by the fibrinolytic pattern. This can be identified either by means of the study of spontaneous fibrinolysis or by means of streptokinase activation (fig. 7). Both procedures are suitable for thromboelastographic investigation. The study of spontaneous fibrinolysis is, however, most significant, insofar as it gives a self-evident demonstration of the phenomenon. Increased fibrinolytic activity with hemorrhagic disorders is often observed in fibrinolytic shock, which may be due to various causes (traumatic, operative, pharmacological, etc.). Thoracic surgery and obstetrical diseases (abruptio placentae, abortion syndromes, etc.) are frequently implied therein.

Special Procedures for Further Evaluation of the Thromboelastographic Data. The thromboelastographic data that characterize the three typical patterns described can be further analyzed by means of certain special procedures, thus making possible more complete identification of the coagulation defects.

One possibility is presented by the addition of normal plasma to the plasma to be tested. This procedure may be used for the analysis of the three fundamental thromboelastographic patterns, i.e., the hemophilic, the thrombocytopenic, and the fibrinolytic types.

In analysis of the hemophilic type, the procedure is similar to the so-called screening tests that are performed in routine coagulation studies. If a minute amount of normal plasma is added in vitro to hemophilic plasma, there is complete or almost complete normalization of the thromboelastographic patterns, as well as for the whole blood coagulation time. As is well known, this does not imply a complete normalization of the coagulation defect, for this is often only slightly modified. The same is true for the modifications that occur after transfusion of blood or plasma

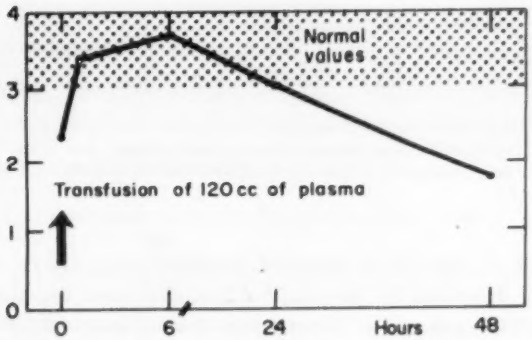

FIG. 8. Modifications of the thromboelastographic index (reaction time plus clot formation time: maximal amplitude) in a hemophilic person after transfusion.

(fig. 8) or after the administration of coagulant drugs (e.g., bothrops venom preparation, fig. 9).

When circulating anticoagulants are present, the thromboelastographic patterns do not show significant modifications on addition of minute amounts of normal plasma. The same happens in the presence of heparin during anticoagulant therapy.

A screening procedure is also possible in the presence of a thrombocytopenic pattern in the thromboelastogram, although the results thus obtained have not yet been completely interpreted for diagnostic purposes. Also, the fibrinolytic type is suitable for a screening test by means of thromboelastography. An example of this is seen in a case of spontaneous fibrinolysis due to dextran infusion (fig. 10), in which the mixture of the patient's plasma and a normal plasma brought about a reduction of the coagulation defect.

Special procedures should be used for further analysis of the thrombocytopenic pattern. Three procedures in particular should be mentioned, i.e., study of the

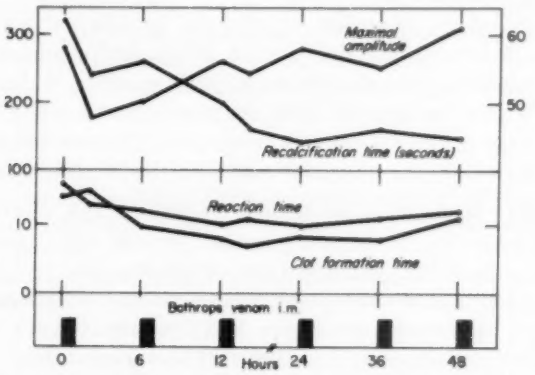

FIG. 9. Modifications of the thromboelastographic components and of the recalcification time in a hemophilic person after intramuscular administration of a Bothrops venom preparation.

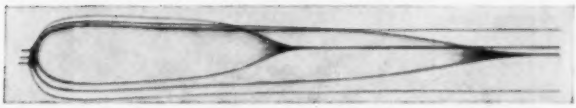

FIG. 10. Thromboelastograms of normal plasma (below), of a mixture of normal plasma and plasma from a subject with fibrinolytic shock due to dextran infusion (intermediate), and of the latter plasma (top). (From: DE NICOLA, P.: La trasfusione di sangue e derivati nei difetti di coagulazione, Pavia, Italy, Edizioni di Haematologica, 1958.)

osmotic resistance of platelets by means of thromboelastography, "rotation thromboelastography," described by Jürgens,[22] differential centrifugation, described by Pratesi et al.[23, 24] In general, all these procedures are based on the fact that platelets may act on the thromboelastogram through the following mechanisms: by releasing platelet factor III (thromboplastic factor) during the disintegration of platelets (although an actual disintegration was questioned), and thus causing a shortening of the reaction time, and by increasing the adhesiveness and resistance of the fibrin threads, thus increasing the maximal amplitude—this happens only when platelets are not yet disintegrated.

In the test for the study of osmotic resistance, these two mechanisms can easily be identified if a platelet suspension is added to platelet-free plasma, with a prolonged reaction time and a reduced maximal amplitude. Until platelets are intact, i.e., not lysed by hypotonic solutions, the maximal amplitude is normalized, but the reaction time is long. As soon as platelets are lysed, there is shortening of the reaction time, but the maximal amplitude is not normalized or may even be unmodified.

The test for the osmotic resistance of platelets has been applied so far to only a few conditions, and it deserves further experimentation. "Rotation thromboelastography" is simpler and makes it possible to identify an increase of the maximal amplitude and a shortening of the reaction time after rotation, in a special "rotator," as a sign of platelet functional activity. In the presence of so-called thrombasthenia or thrombocytopathy, there is no increase of the maximal amplitude, even though the reaction time is shortened.

Finally, differential centrifugation is performed by submitting the plasma to be tested to slow, short centrifugation and to quick, prolonged centrifugation, respectively. By comparing the thromboelastograms obtained in the two conditions, useful information may be obtained about the platelet functional activity.

SUMMARY

A general survey of thromboelastography in hemorrhagic diseases is presented, with particular respect to the following factors: general significance of the thromboelastographic components (reaction time, clot formation time, maximal amplitude, lysis time), typical thromboelastographic patterns in coagulation disorders (hemophilic type, thrombocytopenic type, and fibrinolytic type), and special procedures for further evaluation of the thromboelastographic data (screening tests, osmotic resistance of platelets, rotation thromboelastography, differential centrifugation for the study of platelet functional activity).

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The Management of Anticoagulant Therapy

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The use of anticoagulant therapy has increased from a limited application in the short-term therapy of hospitalized patients to widespread use in the long-term management of nonhospitalized patients. This has resulted in part from accumulation of evidence suggesting that anticoagulants may prolong life in a variety of thromboembolic diseases. Even under excellent hospital conditions, where drug administration and laboratory techniques are well standardized, control is often difficult and hemorrhages are disturbingly frequent and unpredictable. The problem of maintaining smooth, safe anticoagulant therapy is increased many-fold in the ambulatory patient. He must remember to take the proper number of pills at the correct time and to appear at a designated laboratory at frequent intervals. Meanwhile he is leading a "normal" life full of irregularities of activity and nutrition, the effect of which on his anticoagulant status may be considerable. It is incumbent upon the physician who plans to offer this form of therapy to his patients to gain a detailed knowledge of the pharmacology of anticoagulants and of the laboratory techniques used to measure their effects. In addition, the regulation of dosage requires considerable thought and judgment, and the ever-present danger of hemorrhage demands close supervision. The casual use of these drugs in nonhospitalized patients may entail a risk that exceeds the potential benefits.

HEPARIN

Heparin is a mixture of mucoitin polysulfuric acids, probably secreted by mast cells and found in highest concentration in liver and lung tissue. It is the strongest organic acid normally found in the body and its anticoagulant effect is probably related to its strong electronegative charge. The effect of heparin on the clotting mechanism is complex. Antithrombin, antiprothrombin, and antithromboplastin properties have been demonstrated, and it appears likely that heparin blocks several enzymatic reactions.[1] There is a rather wide margin between antithrombotic and hemorrhagic levels of heparin. In addition to its action on the clotting mechanism, heparin affects lipid transport and metabolism. Fragmentary evidence exists that suggests that heparin, by virtue of its effect on lipid metabolism, may retard the progress of the atherosclerotic process. In contrast to the anticoagulant effect, which is brief (hours), the alteration in lipid metabolism is prolonged (days) and

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demonstrable with low doses, which exert little anticoagulant effect. This aspect of heparin therapy must be considered experimental at the present time, and general use of heparin for its effect on lipid metabolism cannot be recommended on the basis of the evidence currently available.

Heparin is safe, effective, and rapid in onset of action and dissipation. It would be the anticoagulant of choice were it not for its expense, the need for parenteral administration, and the frequency of reaction at the site of injection. Because of these disadvantages, heparin is generally used only in patients in whom the need to restore the clotting mechanism rapidly may be anticipated, when an immediate anticoagulant effect is desired, or for short periods of time during the induction of anticoagulant therapy with prothrombinopenic drugs. Rapid induction of anticoagulant therapy is desirable in the presence of thrombophlebitis, pulmonary embolism, or peripheral thrombosis or embolism. We do not feel that it is necessary to use heparin routinely in acute myocardial infarction, since thromboembolic complications are rare in the first 48 hours. If diagnosis or treatment has been delayed, heparin should be used initially.

Heparin may be administered in several forms. We prefer the use of concentrated aqueous heparin (100 mg./ml.) administered subcutaneously. In the average patient, treatment is begun with 150 mg. every 12 hours, although a smaller initial dose is used in older, malnourished, and chronically ill patients. A Lee-White clotting time is performed just prior to the administration of the next dose at the time when the heparin effect is least, and an attempt is made to keep the clotting time to two to three times normal. Occasionally the dosage interval may have to be decreased to eight hours, or the dose increased before control is achieved. It is our practice to obtain one clotting time determination daily during the first few days of heparin therapy and then reduce the frequency of the determination as a stable maintenance dose is established. If prothrombinopenic drugs are to be administered concurrently, the dose of heparin should be given at least six hours before blood is withdrawn for the prothrombin activity determination, since heparin has a tendency to prolong the one-stage determination in an unpredictable manner.

Untoward reactions to heparin are infrequent. Rare cases of allergic or anaphylactic reactions have been reported. Alopecia is an uncommon complication, usually reversible after withdrawal of the drug. Hemorrhage, except at the site of injection, is uncommon because of the wide margin between therapeutic and toxic levels. Heparin is neutralized by equivalent amounts of such positively charged substances as protamine sulfate. If bleeding occurs, the anticoagulant effect of heparin can be immediately reversed by the intravenous administration of 50 mg. of protamine sulphate. This may have to be repeated after several hours.

PROTHROMBINOPENIC DRUGS

Anticoagulants that act by depression of prothrombin activity have the advantages that they are inexpensive and can be administered orally. They are somewhat slower in onset of action than heparin, are more persistent in their effect, and the incidence of undesirable effects, chiefly hemorrhage, is significant. Since the intro-

TABLE I

Properties of Commonly Used Prothrombinopenic Drugs

Preparation	Peak effect, hours after oral administration	Recommended induction (first day), dose, mg.	Average maintenance dose, mg.
Bishydroxycoumarin	40	650	90
Phenindione	32	500	100
Warfarin	48	75	8
Diphenadione	40	60	7
Acenocoumarin	32	28	3
Anisindione	36	500	125

duction of bishydroxycoumarin in 1941, many other preparations have been synthesized. Some of these preparations, such as warfarin and acenocoumarin, are closely related chemically to bishydroxycoumarin. Others, such as phenindione, diphenadione, and anisindione, are synthetic derivatives of indandione, a compound whose biological properties are similar to those of the coumarins. Although each of the newer drugs has been advocated in turn as the "ideal anticoagulant," in carefully controlled studies none of them has been shown to be clearly superior to bishydroxycoumarin.[2–8] The pharmacological properties of the drugs are quite similar. They differ only slightly from each other in respect to speed of onset of demonstrable action, time of peak effect, and dissipation (table I). Warfarin has the minor but distinct advantage of being available as a stable sodium salt, which is suitable for parenteral administration to patients unable to take medication by the oral route. We advise that the practicing physician become thoroughly familiar with one or two of these drugs and continue to use them until there is general agreement that a drug has been developed that is really better than those already available. We doubt that such a drug will be introduced in the near future.

All of the coumarin and indandione preparations act by depressing the hepatic synthesis of prothrombin, factor VII (proconvertin), and factor IX (plasma thromboplastin component or Christmas factor). They may also depress the production of factor X (Stuart-Prower factor), but this has not yet been clearly established. The action of these drugs, once thought to influence only prothrombin synthesis, becomes more complex as the mystery of the clotting mechanism is unraveled. Unlike heparin, which is an effective anticoagulant both in vitro and in vivo, with an immediate onset of action, the prothrombinopenic drugs are effective only in vivo, and no effect on the plasma concentration of clotting factors can be demonstrated for at least 12 hours after administration. The peak effect generally occurs about 40 hours after administration.

Until recently, anticoagulant therapy with these agents has been controlled almost exclusively by the one-stage determination of prothrombin activity, introduced by Quick et al in 1934.[9] During the past few years the problem of the laboratory control of anticoagulant therapy has stimulated much interest and controversy. Several newer tests, such as the two-stage prothrombin determination, the P and P test of

Owren, the highly standardized clotting time determination of Mayer, the determination of the true prothrombin activity, and Owren's thrombotest, have been advocated to replace Quick's one-stage procedure. A detailed discussion of these tests is beyond the scope of this paper. Although the one-stage determination of Quick leaves much to be desired, it has the important virtue of simplicity. It has not been demonstrated to our satisfaction that any of the newer techniques, which are all more time consuming, permit better clinical anticoagulant control with a reduced incidence of hemorrhage or thromboembolic complications.

Another important practical aspect of this problem is the choice of a thromboplastin preparation for use in the Quick one-stage determination. It has been known for many years that the value obtained for the prothrombin activity of plasma will vary greatly if measured by the one-stage technique using each of several different thromboplastins.[10] In a study done in our laboratory, six thromboplastins were used to measure the prothrombin activity of 15 samples of plasma obtained from patients on anticoagulant therapy. The difference in measured activity between the least sensitive and most sensitive thromboplastins was more than 100 per cent (table II). It has recently been demonstrated that most commercially available thromboplastins contain factor VII (proconvertin)-like activity. This activity is most marked in thromboplastin extract of brain tissue and least marked in thromboplastin extract of lung tissue. Since factor VII activity is reduced by prothrombinopenic anticoagulants, it appears desirable on theoretical grounds to employ a thromboplastin that is free of factor VII activity and, therefore, more sensitive to changes induced by the drug. Two commercially available reagents that appear

TABLE II

The Prothrombin Activity of 15 Plasmas Drawn from Patients Receiving Bishydroxycoumarin Illustrating Difference in Measured Activity When Two Different Thromboplastins Are Used in Performing the One-Stage Determination

	Prothrombin activity, %	
Plasma	Bacto thromboplastin	Bacto Aplastin
1	75	46
2	40	19
3	25	15
4	30	17
5	75	62
6	63	48
7	80	58
8	19	10
9	22	15
10	11	Less than 10
11	20	Less than 10
12	45	19
13	40	18
14	23	11
15	30	13

to be relatively free of factor VII activity are Acuplastin and Bacto Aplastin. As long as different laboratories use different thromboplastins, results will not be comparable. The practicing physician should ascertain which thromboplastin is used by the laboratories to which he sends his patients and the approximate sensitivity of the reagent to a factor VII deficit. Under no conditions should a patient on long-term anticoagulant therapy be permitted to use more than one laboratory.

A common source of error in the one-stage determination is the use of a dilution curve for the conversion of prothrombin time to percentage of prothrombin activity. In a recent survey of 13 hospital laboratories, the use of a grossly inaccurate dilution curve was found to be the most common explanation for discrepancies observed among the laboratories in the determination of prothrombin activity.[11] It seems unlikely that the technique of all laboratories can be corrected and standardized. This major source of error could be avoided, however, if physicians became accustomed to thinking in terms of seconds rather than percentage. Since 1½ times the prothrombin in time of normal plasma corresponds to about 30 per cent prothrombin activity, and 2½ times the prothrombin time to about 12 per cent prothrombin activity, with almost all thromboplastins, the prothrombin time of patients receiving anticoagulants should be maintained at about twice that of normal plasma. A satisfactory therapeutic range would be from 1½ to 2½ times the prothrombin time of normal plasma. It must be emphasized, however, that normal plasma is plasma obtained from normal subjects, not the artificial plasma standard furnished by the reagent manufacturer.

One of the major disadvantages encountered in the use of bishydroxycoumarin and similar drugs has been the prolonged induction period before an effective anticoagulant level is reached. By using a single initial dose large enough to produce the desired prothrombinopenic effect, and by eliminating the variable rate of excretion of multiple smaller induction doses, therapeutic levels can be attained more rapidly and predictably and with less variation in the size of the induction dose. In addition, by avoiding a prolonged induction period and the resultant overlapping of the effect of induction and maintenance doses, earlier establishment of a stable maintenance dose is possible. This tends to eliminate the wide swings in prothrombin levels often observed in the early days of anticoagulant therapy. Using this program, more than 80 per cent of patients can be brought into the therapeutic range within 40 hours of the initial dose. Our recommended induction dose for a number of the more commonly used drugs is shown in table I. The initial dose should be administered late in the day so that the prothrombin time two days later will correspond to the peak effect of the initial dose (about 40 hours). It is desirable to obtain a prothrombin time before the initial dose, particularly in patients with long-standing congestive heart failure or hepatic or renal disease. In such patients caution must be exercised in the use of a large initial dose. The prothrombin time on the second day is of little value except to pick out the occasional patient who is so sensitive to the prothrombinopenic effect of the drug that he has rapidly dropped to the therapeutic range. In all other patients, an average maintenance dose is given on the second day (table I). Additional dosage is adjusted by the third day or 40-hour prothrombin time, which corresponds to the peak effect of the initial dose.

The size of the maintenance dosage varies greatly from patient to patient and must be determined individually. A stable maintenance dosage is reached more rapidly if the drug is given daily and if dosage changes are small. It should rarely be necessary to withhold the drug entirely or to double the dosage, and such changes tend to produce wide swings of prothrombin activity. Preparations such as diphenadione and acenocoumarin, which are available in tablets of 5 mg. and 1 mg., are frequently easier to work with because fine adjustment of dosage is possible. In hospitalized patients we customarily obtain daily determinations of prothrombin activity until a stable maintenance dosage is established. The frequency of prothrombin determinations is then reduced to three times weekly throughout the remainder of the hospitalization. We have learned that care must be exercised in the interpretation of "week-end" prothrombin times if they are done by different or less experienced personnel, and changes of dosage based on them should be avoided if possible. It is unwise to accept as correct a sudden change in prothrombin activity in a patient who has been on a stable maintenance dosage for several days. The laboratory determination should be repeated on a fresh sample of plasma before the dosage is changed, particularly in nonhospitalized patients on long-term anticoagulant therapy. An occasional patient will be encountered whose maintenance dosage requirement suddenly changes. In most cases the reason for the change will be obscure. It may be related to the concurrent administration of another drug, such as aspirin, barbiturates, alcohol, xanthines, antibiotics, phenylbutazone, or ataraxics, which may affect the clotting mechanism or alter the dosage requirements of the anticoagulant. Even in apparently stable patients on long-term therapy, the prothrombin activity should be measured at least every two weeks.

The management of patients on long-term anticoagulant therapy is difficult unless the patient is intelligent and cooperative. He must understand the purpose of the therapy, the need for continuous and careful medical supervision, the importance of taking the medicine as prescribed without fail, and the danger of bleeding, which may develop either spontaneously or with minor trauma. Even the most careful patient will occasionally forget whether he has taken his medication, unless some reminder is employed. One method is to have the patient initial the date on a calendar as he takes his daily medication. Errors in dosage and fluctuation in prothrombin activity can best be avoided if the patient is on a uniform daily dosage. Such a regimen can nearly always be established and is more likely to be successful than a program that requires alternating or omitting doses. The patient should be required to carry a card, indicating that he is taking anticoagulant and outlining emergency therapy. The appearance of blood in vomitus, stool, and urine should be described to the patient. He should be given a supply of 5 mg. tablets of vitamin K_1 oxide with instructions to take one for bleeding if he is unable to reach his physician and to go to the nearest hospital if the amount of bleeding is great.

Nonhemorrhagic complications are infrequently encountered with prothrombinopenic drugs. Nausea, vomiting, and diarrhea are occasionally induced by large doses of bishydroxycoumarin, rarely by any of the other drugs. Fever, scarlatiniform eruption, and agranulocytosis have been produced by phenindione.[12] The incidence of this complication is very low and the agranulocytosis is preceded by the eruption

and fever, so that the drug can be withdrawn before irreversible damage is done to the bone marrow if one is aware of the possibility.

The incidence of major hemorrhage in hospitalized patients is about 2 per cent, the incidence of minor hemorrhage about 6 per cent. In well-selected and supervised outpatients, the incidence of hemorrhage should be lower because a stable maintenance dosage has previously been established. The incidence of hemorrhage will probably be much higher in poorly selected and supervised outpatients. The most common sites of hemorrhage are the genitourinary tract, the skin, the gastrointestinal tract, the nose, and the bronchial tree. Minor bleeding from the gums on vigorous brushing is so common that we do not consider it a hemorrhagic complication. There is a rough correlation between excessive prolongation of the prothrombin time and bleeding, but most patients with excessively prolonged prothrombin times do not bleed and many patients who bleed are within the therapeutic range at the time of the bleeding episode.

We rarely find it necessary to use vitamin K_1 oxide. If the prothrombin activity is reduced beyond the therapeutic range without bleeding, we reduce the dosage of the drug for a few days. In the presence of minor bleeding, the dosage should be reduced or the drug withheld for a day or two, depending on the extent to which the prothrombin level is depressed. If bleeding persists, a small oral dose of vitamin K_1 oxide (5 to 10 mg.) may be given. Only in the presence of major hemorrhage do we use large doses of intravenously administered vitamin K_1 oxide. If genitourinary or gastrointestinal bleeding occurs in a patient whose prothrombin time is not excessively prolonged, particularly if the bleeding is persistent or recurrent, a search should be made for a lesion within the organ system from which the bleeding originates.

It has been suggested by some investigators that sudden withdrawal of anticoagulants, particularly in patients who have been on therapy for a prolonged period of time, is followed by a hypercoagulable state and an increased incidence of thromboembolism.[13] They have suggested, therefore, that drug withdrawal should be gradual, when possible, preferably over a period of several weeks.

CONCLUSION

A safe and effective anticoagulant program can be accomplished in both short-term and long-term therapy by the use of one of a group of coumarin and indandione derivatives, with or without initial heparin therapy. Used judiciously, such a program may be instrumental in preventing further morbidity and mortality in a variety of thromboembolic diseases.

Successful use of this form of therapy requires an awareness on the part of the physician of the limitations and dangers inherent in the use of the anticoagulant agents.and intelligent cooperation on the part of the patient.

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BOOK REVIEWS

Medical Science and Space Travel. WILLIAM A. KINNEY. New York, Franklin Watts, Inc., 1959. Pp. 150. Price $3.95.

The major feature of this book are the dozens of fascinating photographs of men being tested under various "space flight" conditions, of animal experiments, of the equipment used in space studies.

The text describes studies of the reaction of the human body to the alien environment of space and the progress of medical science in making it possible for man to survive in such an environment.

The book is a rather superficial review of the subject, intended for the layman and therefore somewhat "written down." It should be read only as a perfunctory introduction to this important subject.

The Mind of the Murderer. MANFRED S. GUTTMACHER, M.D. New York, Farrar, Straus & Cudahy, Inc., 1960. Pp. 244. Price $4.50.

This book, winner of the sixth Isaac Ray Award of the American Psychiatric Association, is an important contribution to the study of the personality of the murderer.

In the first part of the book, the author discusses various types of murderers, based on his study of more than 200 whom he has examined. He probes the mind of the "normal," the schizophrenic, the homosexual, the sadistic, and other murderers, noting that he has found a "stimulating challenge" in the study of criminals as a group and particularly murderers. He writes: "One keeps continually asking why—why—why—and sometimes one gets a satisfying answer."

In the second part of the book, Dr. Guttmacher discusses expert testimony, particularly psychiatric testimony. Here he explains why many physicians try to avoid testifying in court. The last part of the book deals with the patient's right to secrecy and the threat to the confidential physician-patient relationship by the courts.

The sympathetic, understanding approach of the author is revealed clearly in this book, which represents a valuable contribution to improved relations between psychiatry and the law.

Drugs and the Mind. ROBERT S. DE ROPP. New York, Grove Press, Inc., 1960. Pp. 310. Price $1.95.

The story of man's age-old fascination with agents capable of altering his state of emotions and consciousness is reported with great skill in this book. The world of ancient herbs and modern drugs and the joys and tortures that may be experienced through their use is revealed through case reports, anecdotes, statistics, and, especially, interesting quotations from users of the drugs.

Thus we find here a description of the "virtues" of mescal intoxication by Havelock Ellis, Baudelaire's explanation of the world of hashish, De Quincey's famous account of his use of opium (" ' . . . Here was a panacea, a *pharmakon nepenthes* for all human woes; here was the secret of happiness, about which philosophers had disputed for so many ages, at once discovered; happiness might now be bought for a penny, and carried in the waistcoat pocket; portable ecstasies might be corked up in a pint bottle, and peace of mind could be sent down by the mail.' ")

The author brings his fabulous tale up to date with a discussion of LSD, some of the ataraxics, and the psychic anergizers. He concludes on a serious note—a conviction that modern research on these drugs and on the human brain may determine "the future progress, perhaps even the future survival, of man"—and he expresses the hope that progress in this area may help us "to reach spiritual maturity before we destroy ourselves."

Call the Doctor. E. S. TURNER. New York, St. Martin's Press, Inc., 1959. Pp. 320. Price $3.95.

This book, described as "an intimate history of medical practitioners from 1300 to the present," purports to portray a social history of the general practitioner and the surgeon from the days of Chaucer's doctors—the three great Johns: John of Gaddesden, John Mirfeld, and John of Arderne—until the introduction of the National Health Service Bill by Mr. Aneurin Bevan, in March, 1946.

The author, an enlightened and witty contributor to *Punch*, traces the evolution of the medical practitioner through centuries of learning and dogmatism, experiment and quackery, with deliberate emphasis on British physicians. This is probably why this semihumorous lively book is not completely satisfactory. Medicine is an inseparable whole. Its story cannot be done full justice if only the men and events of one country are presented, particularly if the author claims that his story includes the full evolution of medicine during six hundred years. Besides, the history of medicine is history, but it is also *medicine*, and as such it cannot be done justice by laymen—even if they are as erudite as the author—but only by physician-historians.

Nevertheless, some may enjoy this book, scholarly in a disheveled way, brimming with prejudice, but amazingly informative, and containing amusing, little-known illustrations, which charmingly present the laughter wrinkles on the serious face of medicine.—*Félix Martí-Ibáñez, M.D.*

That the Patient May Know: An Atlas For Use by the Physician in Explaining to the Patient. HARRY F. DOWLING, M.D., SC.D., AND TOM JONES, B.F.A. Philadelphia and London, W. B. Saunders Company, 1959. Pp. 139.

This unusual and most attractive book consists of a group of diagrams for use by the physician in explaining to his patients the anatomical relationships and physiological processes relating to various syndromes and diseases. The diagrams are arranged according to organ systems, e.g., the respiratory tract, the cardiovascular system, the gastrointestinal system. Particularly worth while is the chapter on nutrition, metabolism, and growth, which includes diagrams showing how to ad-

minister insulin and the absorption of foods and an explanation of the exchange diet plan for diabetic persons.

As the authors explain, the book is not intended for use by the patient alone, since the text is not fully explanatory, but should rather be used by the physician in aiding the patient to understand his condition.

The diagrams are all clear and simple. This book is novel and should appeal to most general practitioners interested in fullest and lucid communication with their patients.

Current Therapy. S. L. ROY. Calcutta, Indian Medical Journal, 1958. Pp. 240. Price Rs 6.00.

This book is a compilation of articles that originally appeared in the current therapy section of the *Indian Medical Journal*. Written by Dr. S. L. Roy, coeditor of the *Journal*, these articles form a fine review of current therapy for general practitioners in India. The articles cover lipotropic agents, hormones, broad-spectrum antibiotics, therapy of leprosy, anemia, epilepsy, and filariasis, use of radioactive isotopes in medicine, insulin, and other subjects. The author discusses dosage, indications, and other considerations of each drug. Combination therapy is also described where applicable.

The book is exceptionally well organized, concise, and a valuable guide for the general practitioner.

Medical Discoveries: Who and When. J. E. SCHMIDT. Springfield, Ill., Charles® C Thomas, 1959. Pp. 555. Price $14.75.

This excellent dictionary lists more than 6000 major discoveries in medicine and related fields. Each entry cites the name of the discoverer or inventor, his nationality, occupation, birth and death dates, date of the discovery, and explanatory remarks.

To mention just a few of the many fascinating items, we learn that diphtheria was recognized and described as early as the second century, that a sign language for deaf-mutes was devised in 1616 by an Italian physician, that a starvation treatment for diabetes mellitus was introduced in the early twentieth century, that an experiment in transmission of human breast cancer to a dog was attempted in 1774, that fresh air was advocated as an adjunct to hygiene by Benjamin Franklin, that the earliest mention of hemophilia is made in the Talmud, where it is recorded that an infant with hemophilia was exempted from the ritual of circumcision.

Interesting is the fact that some important discoveries were made by men in fields completely unrelated to medicine: the first satisfactory laryngoscope was devised by a Spanish singing teacher, the intermaxillary bone was discovered by the German poet Goethe, the first attempt to catheterize the auditory tube was made by a French postmaster.

This book will be a great aid to all students of medical history. The only drawback to the dictionary is a large number of typographical errors, which should be corrected if a revised edition is published in the future.

INTESTINAL BLOATING. Approximately 75 per cent of a group of 200 patients with excessive gastrointestinal gas not relieved by other measures obtained good to excellent results with a silicone compound, methyl polysiloxane (Mylicon, Stuart), according to a report to the recent American Medical Association annual meeting. The compound alters surface tension of stomach gas bubbles, enabling them to coalesce and be eliminated more easily.

FLUORIDE CONCENTRATE MARKETED. A sodium fluoride concentrate has been placed on the market for the dental protection of persons whose water supplies do not contain fluorine. The liquid is now available in New York, New Jersey, Oregon, Washington, Massachusetts, Nebraska, Michigan, and southern California. Introduced by Crookes-Barnes Laboratories, Wayne, N. J., the liquid is available through prescription by a physician or dentist for adding to beverages in the home.

DIAGNOSTIC TEST FOR AMYLOIDOSIS. Evans blue dye, used for many years to determine plasma volume, has been found to be removed abnormally fast from the plasma of patients with either primary or secondary amyloidosis (Lancet 1: 1007, 1960). Amyloidosis can be diagnosed if the serum concentration of Evans blue at 15 minutes is less than 80 per cent of the concentration at four minutes. An alternate method is determination of the I^{131} human albumin curve (not affected in amyloidosis) and the Evans blue curve simultaneously.

THYROID CARCINOMA. Surgical treatment of occult papillary carcinoma of the thyroid with or without nodal metastasis gave a high rate of cure (J. Clin. Endocrinol. 20:89, 1960). In 140 patients, no evidence of distant metastasis or residual carcinoma was found up to 30 years after surgery. Only 15 patients died during the observation period, and the deaths were unrelated to the thyroid carcinoma.

IRON DEFICIENCY ANEMIAS. Tablets containing 200 mg. of the iron salt ferrous fumarate (Ircon, Lakeside) each provide the equivalent of 65 mg. of elemental iron. Ferrous fumarate is said to be much less toxic in massive doses than other widely used iron salts. The drug is indicated for prophylaxis and treatment of iron deficiency anemias

resulting from inadequate iron intake or from blood loss. The drug should be used with care in the presence of peptic ulcer, regional enteritis, and ulcerative colitis.

SPINAL CORD HYPOTHERMIA. A new technique produces selective hypothermia of the spinal cord in an otherwise intact and normothermic body, it was reported to the recent congress of the Pan American Medical Association. The technique lends itself to the rapid production of very low temperatures with ranges not attainable with other methods. The selective action of the technique offers protection against permanent spinal cord damage from ischemia.

OCCULT BLOOD DIAGNOSIS. A simple, one-minute diagnostic test (marketed as Hemocult by Schieffelin, New York City) to detect occult blood in feces and urine utilizes pure electrophoresis paper impregnated with stable guaiac gum. A 100-inch-long strip of the paper, in a convenient plastic dispenser, is sufficient for 100 tests.

STAPES MOBILIZATION FOR OTOSCLEROSIS. Stapes mobilization for otosclerosis gives a good chance for incapacitated aviators to return to flying duty, whereas fenestration definitely prohibits such activity, according to a report to the Society of Air Force Clinical Surgeons. Stapes mobilization was performed in 25 flyers, with improvement in all: 15 had a return to social hearing, becoming eligible for active duty; 8 could hear above 30 decibels; 2 achieved a 32-decibel level, at which their hearing aids were able to work more effectively.

DERMATOLOGICAL SCARS. An average of six monthly treatments with liquid nitrogen produced moderate to excellent response in a majority of patients with acne scars and active acne, according to a report at the American Medical Association meeting. Also treated with good to excellent response were 56 patients with a total of 424 warts and 26 patients with a total of several hundred keratoses. Other dermatoses that responded well to liquid nitrogen therapy included leukoplakia, neurodermatitis plaques, nevi, chloasma, hypertrophic scars.

ANTIALLERGIC AGENT. A new compound indicated for a wide range of allergic conditions and for pruritus resulting from either allergic or nonallergic conditions is methdilazine hydrochloride (Tacaryl, Mead Johnson). The compound is said to provide prompt and prolonged relief through sustained action at the cellular level. In studies to date, side effects have been minimal.

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FOREWORD: A New Policy

The objective of the QUARTERLY REVIEW OF OPHTHALMOLOGY is to bring together in one publication a concise record of current happenings, both national and international, in this field. Selection and editing of material are designed to prove informative to *the entire medical profession* as well as to ophthalmologists. Manuscripts for the QUARTERLY REVIEW OF OPHTHALMOLOGY should be submitted to Dr. Arnold S. Breakey, Ophthalmological Foundation, 111 East 59th St., New York, N. Y.

The Triumvirate of the Golden Age of Ophthalmology

von Graefe, Donders, Bowman

George E. Arrington, Jr., M.D.

RICHMOND, VA.

Indisputably, the golden age of ophthalmology, i.e., its period of greatest practical clinical growth, was the second half of the nineteenth century. The figures whose names were just listed played the most significant roles in that era and we still await their equals in individual depth and magnitude of contributions to the science and art of ophthalmology. Indeed it is to Albrecht von Graefe that we owe the general character of the practice, to Cornelis Donders that we owe the physiological optical and refractive characteristics, and to Sir William Bowman that we owe a thorough anatomical understanding of ophthalmology. Thus armed with modern ophthalmological anatomy and physiology and consequently with many new medical and surgical therapeutic techniques (mostly discovered or created by our three subjects), ophthalmic practice sprang into full bloom. Rapidly it became respected as a separate but integrated discipline of medicine. It is enlightening and humbling to acknowledge the many great ideas of these truly outstanding men. Concepts such as iridectomy for glaucoma (von Graefe, 1857), the relationship of accommodation to convergence (Donders, 1848), and graded tactile ocular tension (Bowman, 1862) serve along with a multitude of others to illustrate our debt to these three men.

The term "triumvirate" is particularly appropriate, for these three men, in truth, were united as exponents of the highest medicoscientific attributes of mutual personal respect, friendship, and intellectual reinforcement transcending political, nationalistic, and ideological boundaries. Certainly in these times we should look for strengthening of such admirable traits among scholar-physicians of all nations. Science, that is to say knowledge, always supersedes nationalistic interests anyway, and those men who recognize this fact and strive to maintain freedom of the individual thinker in their personal relationships with colleagues around the world do much to cancel petty boundaries and to perpetuate higher and more worthy interests.

Thus was formed the friendship between von Graefe, the German, Donders, the Dutchman, and Bowman, the Englishman. Each was great in his sphere, but again, the sum of their contributions—modern ophthalmology—was greater than the parts.

EDITOR'S NOTE: This is the continuation of a series of articles on contributions to ophthalmology. Dr. Arrington is eminently qualified for the task for he has made a prolonged study of the subject and has written *A History of Ophthalmology* (New York, MD Publications, Inc., 1959).

Albrecht von Graefe (1828–1870) was born in Berlin. His father, Carl Ferdinand von Graefe, was professor of surgery at the University of Berlin and practiced ophthalmology in addition to general surgery, as was the custom then. He was distinguished in his own right, but the distinction of the son eclipsed that of the father. The von Graefe home was that of a wealthy, ennobled physician, and Albrecht received the attentions due a boy of his estate. Albrecht's intelligence was soon in evidence. He graduated from the French Gymnasium at 15 years of age, the youngest person ever to do so. He then attended the University of Berlin, where he came into the orbit of Johannes Müller, the physiologist who made vast contributions to ophthalmological physiology.[1] Like Helmholtz, du Boise-Reymond, Virchow, Schwann, and Brücke before him, von Graefe too was inspired by this great teacher, whose views of vision were actually his views of life itself. Von Graefe was graduated with the doctor's degree Aug. 21, 1847, at the age of 19. After his graduation he traveled for two years, studying with many renowned medical figures, including von Arlt in Prague, who influenced him to become an ophthalmologist, Claude Bernard and Desmarres in Paris, Sichel in Frankfurt, and Rokitansky, Brücke, Jäger, and others in Vienna. He met Sir William Bowman in London, William R. Wilde in Dublin, and William MacKenzie in Glasgow. Finally, von Graefe returned to Berlin.

Von Graefe saw very early that ophthalmology embraces certain technical refinements and details of management totally foreign to general surgery, although ophthalmology shares the same basic concepts of practice. Thus, he set out to establish ophthalmology as a separate and equally important specialty. He also recognized that ophthalmology is inherently medical as well as surgical and he even noted its close relationship to neurology and predicted what was to become psychiatry and psychology. His way was thorny indeed toward the goal of acceptance of ophthalmology as a separate medical doctrine equal to and indeed broader than general surgery because of its medical and optical implications. Despite his great international recognition as an ophthalmologist of the highest caliber, von Graefe was not allowed to lecture or practice in his alma mater, the University of Berlin, until two years before his death. This was due, as Ullman[7] has pointed out, to the jealousy of his former professor of surgery, Juengken, who was also director of the Charité hospital. In consequence, in 1850 von Graefe established his own clinic, at 46 Karlstrasse, in which he served rich and poor alike throughout his tragically short life and where many foreign pupils came to study under him. Ironically, at first German students were prevented from attending his clinic lectures because they were not held at the university.

Von Graefe's international fame grew and his wisdom spread through the *Archiv für Ophthalmologie*, which he founded in 1855 when he was 26 years old, being joined in its editorship by von Arlt and Donders. In the pages of that journal one finds reports of von Graefe's many important discoveries and descriptions, including iridectomy for iritis and glaucoma (1855–1862), improvement in cataract surgery (1865–1868), the recognition of optic neuritis as the cause of blindness (1860), and the diagnosis of blindness due to embolism of the central retinal artery (1859). During the years 1874 to 1880, with Edwin Saemisch, von Graefe wrote his *Hand-*

buch der Gesammten Augenheilkunde in seven volumes, possibly the greatest textbook of ophthalmology ever written.

Von Graefe's name is linked with the diagnosis of exophthalmic goiter in his sign of lid lag on looking down (Graefe's sign), with progressive ophthalmoplegia (Graefe's disease), and with the linear cataract extraction knife (Graefe's knife).

He studied many varied ophthalmic problems, such as the effects of atropine, the diagnostic value of visual fields, strabismus, noninflammatory corneal thinning, and pigmentary degeneration of the retina, and he invented a phakoscope and an ophthalmometer. In the field of eye muscle disorders, he wrote *Symptomenlehre der Augenmuskellähmungen* (Berlin, 1867).

In August, 1851, von Graefe met Donders at Bowman's house in England and the triumvirate was established, to be broken only by von Graefe's death due to tuberculosis in 1870.

Sir William Bowman was born in Nantwich, England, July 20, 1816. He studied medicine in Birmingham for five years, becoming demonstrator of anatomy at King's College Hospital in 1834 when he was only 18 years old. His early association with anatomy certainly shaped the general character of his life's work, which included numerous contributions to ocular and general anatomy. His first treatise dealt with the minute structure and movement of muscles (1841–1842), and he then wrote "On the Structure and Use of the Malpighian Bodies of the Kidney" in which Bowman's capsule is described.

At the age of 24, he became surgeon at King's College Hospital, but he soon turned exclusively to ophthalmology, becoming the leading English ophthalmologist. In 1843 he became assistant surgeon at the Royal London Ophthalmic Hospital and in 1850, full surgeon.

Bowman brought his powers of anatomical observation into ophthalmology, describing the anterior elastic lamina of the cornea (Bowman's membrane), the corneal interspaces (Bowman's tubes), the muscularity of the ciliary body (independently and concurrent with Brücke), and the true nature of the lamellar cataract. Bowman invented lachrymal probes, a lens scoop, an iris hook, a cutting needle, a syringe for soft cataract, a method for dilating and slitting the canaliculus, and a ptosis operation. He was the first to extract cataract using chloroform anesthesia.

In 1847 he delivered "Lectures on the Parts Concerned in the Operations on the Eye" at the Royal London Ophthalmic Hospital in which he presented much of his ophthalmic anatomy. In 1859 he introduced skiascopy to detect irregular astigmatism, and in 1862 he introduced digital (tactile) tonometry, which he graded plus and minus for the evaluation of glaucoma patients.

Bowman enjoyed a popular practice and his eminence in British ophthalmology was quickly established. When he was 65, he was honored by being elected president of the ophthalmic section of the International Medicine Congress in London (1881). He helped found the British Ophthalmological Society (1880). Bowman died of pneumonia March 29, 1892.

Cornelis Donders was born May 27, 1818, at Tilburg in Noord-Braband, Holland. He studied medicine at the University of Utrecht and later at the University of Leiden, where he received his medical degree in 1840 at the age of 22. Eight years

later he had risen to the rank of extraordinary professor of anatomy and physiology at the University of Utrecht, where he came in contact with problems of physiological optics. He became greatly interested in this subject, which led naturally to an interest in ophthalmology (1852). Three years later he met Bowman and von Graefe. His contributions to his newly chosen field culminated in his classic book, *The Anomalies of Refraction and Accommodation* (1864).

By 1852 he was professor in ordinary in ophthalmology at Utrecht and three years later he became coeditor of the *Graefe Archiv*. In 1858 Donders founded the Eye Hospital for the Netherlands, and in 1866, his physiological laboratory.

Donders contributed to basic understanding of physiological optics, refraction, and accommodation. He related anomalies of refraction to strabismus (1848), and he distinguished between presbyopia and hyperopia (1859). In 1863, he devised an ophthalmometer, the prototype for many later models. He studied *muscae volitantes* (1847) and regeneration of the cornea (1848). Donders died at 70 years of age on March 24, 1889.

Thus these three titans of nineteenth-century ophthalmology joined intellectual forces, reinforced by personal friendship, to make real their vision of ophthalmology as a distinct discipline within medicine, firmly established on scientific grounds, and embracing the completeness of the medical art.

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The Twentieth Century: Its Impact on Ophthalmology

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In earlier vignettes in this series concerning previous centuries, it has been possible to select a few men to represent the major original contributors of the period. However, in discussing ophthalmology in this century, it is not possible to select just a few representative men. In fact, the tremendous increase in the total number of research centers and workers of considerable merit would necessitate citing long lists of names in order to be fair and complete. It is likewise more than likely that even then one might select events and men who by their current popularity appear to be highly significant, only to have the perspective of years prove the selection to be unjustified.

However, recognizing how valuable such an attempt might be to a student of ophthalmological history of the next century, I shall attempt to present for him an evaluation of these recent events and beg my contemporary readers to extend no final judgment of my choice for at least one hundred years.

What was begun at the end of the nineteenth century was continued in the early twentieth century. Thus, the general trend of development of ophthalmological science early in the twentieth century was toward refinement of knowledge about physical ocular measurements and of anatomical, optical, and physiological data, toward cataloging new ocular disease entities, describing pathology, and searching for new therapeutic measures.

One significant influence on the growth of ophthalmic science was the establishment of many excellent institutes for research ophthalmology, such as the Wilmer Institute (1924), the Presbyterian Institute of Ophthalmology, the Institute of Ophthalmology of Columbia University, the Howe Laboratory (1931), the Oscar Johnson Institute, and recently the Francis I. Proctor Laboratory (1954). But we note that it is individual men and especially men with new ideas who affect progress, and not institutions, which, it must be remembered, came into being as the result of individual initiative and achievement.

It is interesting to consider the spirit of the early twentieth century generally in order to try to find any determinative factors of the times that may have influenced the development of ophthalmology. Certain of these assumptions are tempting. At the turn of the century, the gas lights were fading fast, and the first incandescent street lights and model "T" Fords were being used.

Certainly the advent of new and useful electrical and mechanical devices such as these accounts for an increased attention to development of such devices within ophthalmology, but even more, the widespread spirit of investigation and practical application that lay behind those devices permeated science generally, including

medical science. It is appropriate that along with the refinement of everyday technical appliances we find a comparable development of what one might loosely term "gadgetry" in medicine. Thus one finds the appearance of electrical, electronic, and mechanical devices for instance in cardiology (the electrocardiograph, the ballistocardiograph), in neurology (the electroencephalograph), in physical medicine (diathermy), in otology (the audiometer), in endocrinology (radioactive isotopes and Geiger counters), in roentgenology (the million-volt x-ray machine, radioactive cobalt machines), and so forth.

In ophthalmology many highly useful tools emerged, such as the slit-lamp microscope (Gullstrand), the electric ophthalmoscope (Friedenwald, May), perimeters (Ferree-Rand, Harrington), fundus and eye photography (Nordensen, Donaldson, Bedell), and more recently electroretinography, electromyography, sonograms, tonography, and flicker fusion tests.

Always the emphasis in research during this era seemed to rest on application. A disease such as uveitis or glaucoma would be an isolated object of study. Associated research, while basic in nature itself—such as measurement of aqueous outflow, lens metabolism and growth, high energy effects on ocular tissues, microanatomy of the intraocular drainage channels, ocular electrophysiology—was likewise still oriented toward clinical application. Basic study for the sake of knowledge itself has not been adequate justification for support recently and this is in tune with the times. However, it must again be remembered that ultimately any applied science rests on originally disinterested basic research. Moreover, the quick clinical application, while always hoped for, was only seldom achieved.

Thus, we have witnessed a shifting in the character of scientific medical investigations from the patient-centered clinical aspect of the heroic and classical periods of medicine to the disease-organ-physicochemical-centered aspect of the early twentieth century. Perhaps I am bold to say this, but I believe that the pendulum has reached its limits in this respect and that we are beginning to see evidences of a returning regard for the whole, integrated patient. This is true, perhaps even more true, in ophthalmology, which, although it paradoxically appears superficially to be a most narrow field of interest, actually represents a key to a broad entrance into the investigation of certain basic aspects of man in both health and disease. Just as man's emotions, thoughts, and intentions shine in his eyes, so many physiological and pathological aspects of his life are reflected in ocular and visual disturbances, and these facts have come to motivate the thinking of ophthalmological investigators more and more, particularly during this century. This is an uplifting aspect of the "ophthalmological mind" that tends to liberate the specialist so that his true fundamental character as a physician in the best sense can dominate his technology. Ultimately the patient is best served by the physician with the broadest and deepest knowledge. If the whole man can affect vision and if vision can affect the whole man, as I believe studies of this century particularly have shown, then it behooves the ophthalmologist to be a student of the whole man in order to appreciate, understand, and enhance vision.

The groundwork of technical data evolved in past centuries through much labor of many investigators is the necessary foundation for thinking about ocular function

and dysfunction. In the nineteenth century the structure of the specialty as we know it evolved, largely through the influence of Albrecht von Graefe, and this has produced a fairly satisfactory means of implementing the doctrine of ophthalmic science, but the role of twentieth century ophthalmology seems to be to emerge to a new height of comprehending vision and ocular disease within that established specialty structure and based on carefully selected particulars of technical knowledge. It is no longer true that ophthalmology can be dominated by the narrow investigator. While much remains to be known, as will always be true, the times demand integration of knowledge as well as new discoveries.

Medicine generally has changed during this century in another way, and here one cannot help but suspect that while certain value has come of this change, something also has been lost. I refer to the trend toward group investigation, or what one might term "groupism." It is not difficult to identify trends in politics during the twentieth century that depreciated the individual. It does not matter whether these developed as fascism, communism, or socialism, for all share the common role of a threat to the individual. The sacrifice of the identity of the individual is an important force at work in our century, and in medicine it has produced anonymous reports from research groups who must find some security in their anonymity. Security seems to be the keyword of the century; it is the most illusive and most sought-after quality of life, especially when nations are armed and belligerent. We seem to have forgotten today the older sources of security. I refer to inner security based on firm principles, a stable philosophy of life, and an enduring scale of values. The lack of security can be traced to the very materialism that would be the source of security for so many today. In our society, materialism begets commercialism and commercialism begets success and success, completing the cycle, is measured by material gain and possessions. Other values than the values of possession have been all but crowded out. In our hectic search for material success we seem to have forfeited the true bases for security. There is no time to build an enduring philosophy of life and no time for studying and establishing the firm ethical principles from which standpoint one would be united in conviction with others of like mind to fight for what is valuable and against what is established as contrary to those principles. There, in that struggle, one could find the real sources of security, in being united in the pursuit of lasting values. Rather than struggle for this individual liberty in politics, and in science and medicine as well, people of our century have been yielding to the easier road of acceding to authority, of submitting to the will of the group, of delegating duties, and of devaluating the importance of individual achievements.

Another related aspect of materialism in ophthalmology is the effort to establish vision as identical with opticoneurophysiological events. Thus we have witnessed in this century the rise of cerebral localization of vision along with other phenomena. In addition, cybernetics pretends to present the answer to body-mind relationship, and this tendency to introduce mechanical devices such as the computer into diagnosis and therapy is destructive to medicine. But a strong, small voice has persistently opposed this philosophy, declaring, "man is something more, vision is something more." Meanwhile, spurred on by the popularity of the materialistic approach and still stimulated by the age-old curiosity to search for the true self, i.e., the spiritual

and mental as well as the physical manifestations of man, investigators have made remarkable achievements in defining the anatomy, histology, physiological chemistry, physics, and cerebro-ocular relationship of the structures underlying vision. But as knowledge in our era grows more profound, it is seen to emphasize still further the profundity of life functions such as vision. As the limits of the knowledge of the material side of vision have been more closely approached during this century, the insufficiency of even these data to answer the mysteries of vision become more and more clear. Thus the very studies sponsored by the materialistic philosophy are providing the evidence for the inability of that philosophy to supply satisfactory answers. One might project that the future may hold a return to considering the problem of vision on new grounds, namely, intellectual, mental, and logical grounds. Thus the thinking of many great philosophers on vision may regain significance and once again the merits of the historical approach will be realized. Certainly the exact knowledge of the mechanics of the visual mechanism will serve to enlarge the understanding of the ocular tissues in health and disease, but so also will the deeper knowledge of vision itself when considered on its own grounds and its own terms.

In contrast to that approach, the role of science in collectivistic societies may be considered to be tied to dogma, which is futile, and we need not fear it. The free mind can say, "I was right here and wrong there," and then set the wrong part right. The collectivist has no such margin for error. He must reflect the common view. He must fit new facts into outmoded schemes, for to do otherwise means that the schemes were wrong to begin with and that is inadmissible. In the clumsy, faltering, often stumbling but always free society, progress is at least a possibility. Materialism is bounded by its finiteness, but nonmaterial concepts reach out for infinity. Thus the great conflict of our age in ideology extends from philosophy to politics, science, medicine, and thus to all phases of life.

Events of the atomic age have meant potential power over matter to the collectivists and potential aggressive destruction to the individualists. Only recently have those events signaled the individualists to strike a blow at materialism and find strength in the mutability of matter. The free scientific society is finding its own voice at last. Those elements of stifling materialism intruded by dogmatic and even dictatorial circles are being superseded by newer and more brilliant insights into human physiology. We no longer need them, if we ever did. The medical scientist as a man is realizing that "the reconstruction of the consciousness and of self-respect can be achieved only through a system of education. . . . This reconstruction cannot be forcibly accomplished by the conquerors."[1] Castiglioni has realized that events of this century have proved that, "to deprive man of liberty of thought and action is equivalent to denying the organisms the freedom to breathe or to take nourishment."[1] This is certainly equally true of thought in ophthalmology during the twentieth century.

Group efforts have produced a number of valuable results. I refer to the establishment of standards of vision in various occupations, prevention of accidental blindness, prevention of infantile blindness, determination of visual and ocular needs of school children, control of childhood accidents by fireworks and firearms, sight-

saving classes, public surveys to detect glaucoma, and education of blind and near-blind persons—all are outgrowths of collective ophthalmological efforts during the twentieth century. In brief, the group effort sponsored growth of technique and organization, but not growth of the physician as an individual and human figure.

To complete the general picture of twentieth-century ophthalmology, it should be noted that in the clinical phase, studies on psychosomatics, allergies, and focal infections and use of antibiotics and chemotherapeutics represent important new developments. Therapeutic victories of note include those over toxic amblyopia, retrolental fibroplasia, sympathetic ophthalmia, and corneal opacities, as well as new methods for dealing with glaucoma (miotics, carbonic anhydrase inhibitors, surgery), cataract (surgery, zonule-absorbing enzymes), aphakia (aspheric, contact, and implant plastic lenses), refractive errors (contact lenses, surgery, aniseikonic lenses), retinal detachment (surgery, light coagulation, electrocoagulation), uveitis (antibiotics, steroids), pterygium (surgery, irradiation), trachoma (antibiotics, chemotherapeutics), herpes zoster (steroids), herpes simplex (antibiotics), ocular allergy (antihistamines, steroids), macular disease (vitamins, peripheral vasodilators), retinal tumors (irradiation, light coagulation), retrobulbar tumors (irradiation, surgery), muscle imbalances (orthoptics, pleoptics, surgery), and ptosis (surgery).

In summary, twentieth-century medical science including ophthalmology is rich in many technical achievements. However, certain tendencies have surreptitiously increased, such as overemphasis of the group at the expense of the individual, loss of interest in basic research in favor of applied research, loss of inner security, decrease in the value of individual liberty and the willingness to sacrifice for it, and increased material interests and commercialism. Not all black or white, the twentieth century emerges as an era of challenge for free individual initiative in ophthalmological science, as in life in general, by closely ordered collectivism. The future ophthalmic historian will write the final chapter, but we have the privilege to choose and the choice, if made according to the principles of individual research and conduct in matters of science and medical practice, does not promise an immediate reward.

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Abstracts from Abroad

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Mass Treatment of Trachoma: Field Trials of Different Drugs in 10,033 Bantu Children. J. GRAHAM SCOTT. South African M. J. 34:442–444, May 28, 1960.

A team of 10 ophthalmologists collaborated with Dr. Scott in these extensive tests, which were conducted over a large part of the Union of South Africa. Different antiseptics and antibiotics, with and without cortisone, were tried. All treatment was done on school children. All were treated twice daily on three successive days each month for 18 months.

Results. The incidence dropped from 31 to 21 per cent, but the results varied greatly. No further improvement in the following year could be achieved. On the basis of these extensive researches, the following scheme is drawn up for the future treatment of the disease: children in all schools in affected areas should be given mass treatment twice daily, on five consecutive days each month for six months. Uncured patients should continue treatment thereafter on an individual basis. Each new intake of students should be followed by the same pattern of treatment. Native field workers should be appointed to supervise this work under medical guidance and to visit all homes to encourage self-treatment in younger children. 5 references. 1 table.

Trachoma Studies: Transmission of Jane Furse Virus to a Human Volunteer. J. GRAHAM SCOTT, JAMES GEAR, E. CUTHERSON, AND D. M. SMITH. South African M. J. 34:450-451, May 28, 1960.

A volunteer, an adult man 45 years old, who had not previously suffered from a subacute or chronic eye infection, was inoculated in the left eye with a suspension of trachoma virus. This virus had been isolated from a clinical case of trachoma seen at the Jane Furse Hospital in Sekukuniland in the North Eastern Transvaal. The volunteer developed acute conjunctivitis three days after inoculation. His condition showed no spontaneous improvement but continued to evolve. On the twenty-fourth day a pannus was observed. On the thirty-first day treatment was begun. Response was rapid and satisfactory. In laboratory tests the virus particles were always observed in repeated smears. The virus was also established readily in egg cultures from swabs taken at the same time. Typical cytoplasmatic inclusion bodies were regularly found from the sixteenth day onward after inoculation. Virus particles were seen on the third day after treatment was begun but not afterward. Cultures gave negative results on the fifth day after treatment was begun and subsequently. The volunteer remained well for six months, when he was reinfected in the same manner. The course of the infection and the recovery after treatment were the same as the first time. 2 references. 2 tables.

Laboratory Studies of Eye Infections in South Africa. The Properties of the Virus of Trachoma.

E. CUTHERSON, D. M. SMITH, AND JAMES GEAR. South African M. J. *34*:453–456, May 28, 1960.

A virus morphologically resembling the virus of trachoma was isolated in yolk sac cultures in chick embryos. The isolated virus, which came from the eyes of a 7-year-old girl, was called the Jane Furse strain. It has been successfully established in serial passage in yolk sac cultures. The virus particles became numerous from the fourth passage onward. The virus has been passaged weekly. In these passages the yolk sac membrane was harvested and the yolk allowed to drain. The membrane was ground and a 20 per cent suspension prepared in nutrient broth; 0.2 of this was reinoculated into the yolk sac. Smears were made periodically on glass slides. These were fixed in methyl alcohol and stained with Giemsa stain or by Machiavello's method. The elementary bodies had the well-known appearance described previously. The amount of the virus in the yolk sac membrane was determined by titration. Its thermal stabilization was also fixed. It keeps best at −20 C. freeze dried (six months or more). A large number of experiments were made to determine the pathogenicity of the virus suspension in animals. They were all unsuccessful. More than 70 different experiments were made in an attempt to cultivate the trachoma virus in animal tissues. After many unsuccessful trials, the desired preparation was eventually found in tissue cultures prepared from the testes of vervet monkeys (*Cercopithecus pygerythrus*). In the cultures, large numbers of elementary bodies could be found. 3 references.

Laboratory Studies of Eye Infections in South Africa with Special Reference to the Virus of Trachoma. ELINOR WHITNEY AND JAMES GEAR. South African M. J. *34*:451–453, May 28, 1960.

Four expeditions were undertaken in an attempt to isolate trachoma virus from early clinical cases of unhealed trachoma. Conjunctival smears and cultures for virus studies were collected. A cotton swab was rolled over the surface and this was immediately immersed in 1 ml. of broth containing 2000 to 5000 μg. of streptomycin, after which the excess broth was pressed out of the swab and the swab was then used to inoculate a chocolate agar slant and a tube of nutrient broth. Certain cultures were inoculated in the field into yolk sacs of 7-day-old embryonated hen's eggs. These were sealed, immediately transported to the laboratory, and incubated at a temperature of 35 C. Suspensions of the cultures were prepared and used for reinoculation. After some failures, the investigators succeeded in cultivating the virus from typical cases in the neighborhood of the Jane Furse Hospital. It will now be possible to develop diagnostic tests to define exactly the distribution and incidence of this disease in Southern Africa, to determine the relative importance of viral and bacterial infections, and to carry out comparative tests with viruses isolated elsewhere. It will be possible to produce a vaccine, but its value will be determined only by extensive and prolonged field trials. 4 references.

Measurements in a Field Survey of Trachoma Before and After Treatment. A. M. ADELSTEIN. South African M. J. *34*:446–449, May 28, 1960.

This paper describes the results of a survey, conducted by two ophthalmic surgeons, of trachoma in African school children at four schools in the Potgietersrust district of Northern Transvaal. The primary objective was to obtain a measure of the effectiveness of certain routine treatments. In doing so it was necessary to measure the inconsistency in a surgeon's diagnosis from time to time and the differences in diagnosis that two surgeons manifest when examining the same patients. The results were as follows: The mean prevalence of trachoma before treatment was 25 per cent up to the age of 10 years, 13 per cent at age 11 to 14 years, and 11 per cent at age 15 to 18 years. After the surgeons had consulted on a standard, the disagreement was nevertheless substantial, being 13 per cent of all children examined. In a series of 134 patients examined twice in the same afternoon by both surgeons, there was close agreement both within one surgeon's diagnoses and in those of two surgeons. Six months later and without another consultation about standards, the difference was 8.7 per cent. The results of the treatment were not uniform, but there was no doubt about the effectiveness of the antibiotic ointments. Far more important than the type of the antibiotic used is the efficiency and the enthusiasm with which the treatment is carried out. The infection with the disease apparently occurs at a very early age. In the absence of treatment, it becomes chronic. There is a minimum of reinfection at school ages, during which time the prevalence gradually diminishes as the children get older. 7 references. 5 tables.

Grant Made to Yale School of Medicine for Studies on Glaucoma

A grant of $18,689 has been made to the Yale School of Medicine by the Connecticut Lions Eye Research Foundation in support of basic investigations this past year on glaucoma. The grant is the second given to Yale by the Foundation in the past three years. An initial grant of $19,000 was made in May, 1957.

The money contributed by Connecticut Lions is used to support work of the Glaucoma Research Laboratory and of the Department of Anatomy at the Yale School of Medicine. The Glaucoma Research Laboratory at the Yale–New Haven Medical Center was established in October, 1958. Research in this laboratory has been directed toward development of more accurate methods for determining intraocular pressure to facilitate early diagnosis and to study the changes which occur during the course of the disease.

In the Department of Anatomy, research of a more basic nature is concerned with the development of the structural and optical properties of the cornea. The development of the chick embryo cornea has been studied in this laboratory for relationships between structure, interference pattern, and transparency.

ABSTRACTS

35. *Bilateral Retinal Detachment Following Carotid-Cavernous Fistula.* JOHN F. COGAN. Brit. J. Ophth. *44*:185–188, March, 1960.

This is an interesting case report of bilateral exudative retinal detachment occurring as a complication of a carotid-cavernous fistula. The author was unable to find a report of a similar complication in the literature, although retinal detachment after orbital cellulitis has been reported on occasion.

The patient was a 53-year-old woman with a history of pain and redness of the left eye and headache. There was no history of trauma. The left eye was proptosed, the visual acuity was reduced to counting fingers, and the fundus was obscured by the cloudiness of the vitreous. A diagnosis of orbital cellulitis was made and antibiotic therapy was begun. Several days later the right eye became similarly proptosed, and a bruit was heard over the forehead. About three weeks later, bilateral retinal detachment involving the lower segments appeared. No holes could be found. After approximately five months, spontaneous reattachment of the retinas occurred. The visual outcome was excellent, the central vision being 6/12 in the right eye and 6/9 in the left eye.

Presence of an arteriovenous fistula was apparently not confirmed by angiography, but the bruit and the other findings left little doubt that this patient had an arteriovenous fistula and that this was the cause of the original difficulty. The authors express the belief that spontaneous thrombosis of the cavernous sinus closed the fistula and accounted for the disappearance of the bruit and the improvement in vision.—*Thomas P. Kearns, M.D.*

36. *Association Between Maternal Disease During Pregnancy and Myopia in the Child.* PETER A. GARDINER AND GRIFFITH JAMES. Brit. J. Ophth. *44*:172–178, March, 1960.

Congenital myopia has been shown to be associated with prematurity. The authors state that previous studies do not preclude the possibility that the cause of the prematurity is associated also with myopia in the infant.

Although their study dealt with only 76 subjects—37 myopic and 39 nonmyopic—the authors draw the conclusion that congenital myopia occurs far more frequently after pregnancy complicated by serious illness than do other visual defects. Myopia was found four times as frequently as other visual defects in children of mothers with toxemia.—*Thomas P. Kearns, M.D.*

37. *The Central Artery of the Retina. I. Origin and Course.* SOHAN SINGH AND RAMJI DASS. Brit. J. Ophth. *44*:193–212, April, 1960.

This report concerns a post-mortem anatomical study of 106 human orbits. The method of study involved injection of neoprene latex into the arterial system of

the orbit, and dissections were performed on the majority of the specimens; histological sections were made in a few cases.

Of 102 specimens, 96 showed the ophthalmic artery arising from the internal carotid artery in the usual manner. In 4 cases the ophthalmic artery arose from the internal carotid artery, but the major contribution to the blood supply came from the middle meningeal artery. In 2 specimens the ophthalmic artery received all of its blood supply from the middle meningeal artery.

In 2 specimens double central retinal arteries were present; they arose independently from the ophthalmic artery.

The course of the central retinal artery was studied in detail, and three distinct parts (intraorbital, intravaginal, and intraneural) are described and the different variations noted.

From this study it would seem that approximately 2 per cent of the ophthalmic arteries arise from the middle meningeal system, which is a part of the external carotid system. With the increasing use and importance of ophthalmodynamometry, this finding seems to be of considerable importance.—Thomas P. Kearns, M.D.

38. *The Electromyogram from Ocular Muscles in Myasthenia Gravis.* M. L. SEARS, F. B. WALSH, AND R. D. TEASDALL. A.M.A. Arch. Ophth. *63*:791, 1960.

Seven patients are presented. Diagnostic electromyographic features are the progressive decline of electrical activity in sustained ocular muscle contraction and the subsequent recovery after rest or an injection of edrophonium chloride. Irreversible changes in the electromyography pattern occurred in 6 of these patients. This suggests that some degree of myopathy is frequently present as well as the usual myoneural junction disturbances. The associated myopathy may explain the refractory state to anticholinesterase medication, which develops frequently.—*Ralph Z. Levene, M.D.*

39. *Retinal Hemorrhages in the Newborn.* C. L. GILES. Am. J. Ophth. *49*:1011, 1960.

In an effort to determine the incidence of retinal hemorrhages, 100 newborn infants were examined no more than one hour after birth. Retinal hemorrhages occurred in 40 per cent of the cases. The parity of the mother, weight of the infant, duration of labor, anesthetic agents employed, and degree of cyanosis at birth cannot be definitely implicated as main causes. Rapid release of the increased intracranial venous pressure as a result of poor delivery of the head of the infant seems to be a significant factor. The variable time of the first ophthalmological examination of the infant is the probable explanation for the great discrepancy in the reported incidence of retinal hemorrhages in the newborn infant.—*Ralph Z. Levene, M.D.*

40. *The Clinical Application of the Goldmann Applanation Tonometer.* T. A. F. SCHMIDT. Am. J. Ophth. *49*:967, 1960.

The Goldmann tonometer is an applanation device that fits onto a slit lamp. It is simple, convenient, and more accurate than the usual Schiøtz instrument. About

99 per cent of normal intraocular pressures are below 22 mm. of mercury. If the pressure curves show several peaks higher than 23 mm. or more, medical therapy is started. Surgical treatment is advised if the pressure is constantly greater than 26 mm. of mercury despite optimum medical therapy.—*Ralph Z. Levene, M.D.*

41. *Corneal Vascularization.* M. E. LAUGHAM. Am. J. Ophth. *49*:1111, May, 1960.

The influence of a mitotic inhibitor, triethylene thiophosphoramide, on the rate of growth of new vessels into the cornea of the rabbit has been studied. Vascularization was induced with alloxan injected into the anterior chamber. The inhibitor was found to cause a decrease of more than 80 per cent in the rate of ingrowth of new vessels when given intramuscularly, subconjuctivally, or topically.—*Ralph Z. Levene, M.D.*

42. *Pathogenesis of Paralysis of the Third Cranial Nerve.* WILLIAM P. KEEFE, C. WILBUR RUCKER, AND JAMES W. KERNOHAN. A.M.A. Arch. Ophth. *63*:585–592, 1960.

To clarify the mechanism by which the third cranial nerve is interrupted and to establish the site of involvement in various diseases, the authors examined the brains of a number of patients seen at the Mayo clinic who had exhibited impaired function of the nerve during life. The anatomical course and relationships of the nerves are discussed. Although the causes of oculomotor paralysis vary widely, the mechanisms of production of the defects in the nerves and the sites of interruption are common to many of the causes. Representative cases due to various causes are presented with necropsy findings. The most frequent intracranial sites of interruption of the nerve fibers are between the posterior cerebral and the superior cerebellar arteries and against the tentorial shelf. Displacement of the mid-brain and pons by supratentorial pressure results in compression of the nerves by the posterior cerebral arteries. Cerebral edema often is accompanied by herniation of the uncinate gyri, which may result in compression of the oculomotor nerves against the tentorial shelf.—*Garrett L. Sullivan, M.D.*

43. *Ocular Findings in Cystic Fibrosis of the Pancreas.* M. BRUCE GORDON, CAROLYN R. DENNING, AND HAROLD F. SPALTER. A.M.A. Arch. Ophth. *63*:391–401, 1960.

In a preliminary report the authors present the ophthalmoscopic findings in 24 patients with cystic fibrosis of the pancreas. It is the authors' impression that the patients who develop abnormal eye findings have, as a rule, severe pulmonary disease from the time their underlying disease is first identified. Papilledema and venous distention and tortuosity were the most common findings. Retinal hemorrhages were present in less than half the patients. A macular cyst was found in 1, a macular hole in another. The histopathological findings of the eyes from 3 cases are presented. The mechanism of the eye changes is far from clear. These changes are seen only in patients with moderate to severe pulmonary disease who also have elevated concentration of gamma globulin in serum and cerebrospinal fluid.—*Garrett L. Sullivan, M.D.*

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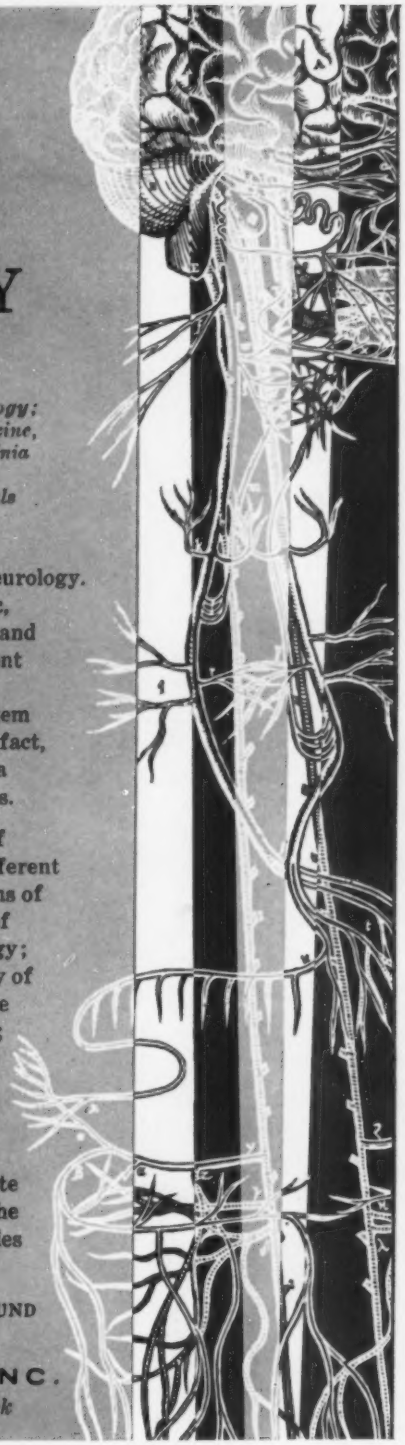

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